Gross motor abilities and interventions in girls and women with Rett syndrome: A literature review; Longitudinal video analysis of gross motor abilities of girls and women with Rett syndrome

Kitty-Rose R. Foley
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Gross Motor Abilities and Interventions in Girls and Women with Rett syndrome: A Literature Review

AND

Longitudinal Video Analysis of Gross Motor Abilities of Girls and Women with Rett Syndrome

Kitty-Rose Foley

A Report Submitted in Partial Requirements for the Award of Bachelor of Occupational Therapy Honours, Faculty of Computing, Health and Science, Edith Cowan University.

Submitted (September, 2009)

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I would like to acknowledge and thank my supervisors Dr Sonya Girdler, Dr Jenny Downs and Dr Helen Leonard for their support and guidance. I would like to thank Ms Ami Bebbington and Mr Peter Jacoby for their assistance with statistical analysis. I would also like to acknowledgement the Telethon Institute for Child Health Research in providing access to data, facilities and support throughout the project. Finally, I would like to acknowledge and thank the effort of the families and carers of the girls and women with Rett syndrome who took the time to participate in this study.
## Table of Contents

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>PAGE NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Article 1: Gross motor abilities and interventions in girls and women</strong></td>
<td></td>
</tr>
<tr>
<td>with Rett syndrome: A literature review</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>5</td>
</tr>
<tr>
<td>Results</td>
<td>6</td>
</tr>
<tr>
<td>- Phenotype genotype correlations in relation to mobility</td>
<td>6</td>
</tr>
<tr>
<td>- Gross motor functioning</td>
<td>9</td>
</tr>
<tr>
<td>· Early development</td>
<td>10</td>
</tr>
<tr>
<td>· Scoliosis</td>
<td>11</td>
</tr>
<tr>
<td>- Outcome measures and tools</td>
<td>12</td>
</tr>
<tr>
<td>- Summary</td>
<td>13</td>
</tr>
<tr>
<td>- Therapy Interventions</td>
<td>13</td>
</tr>
<tr>
<td>- Gross motor intervention research in Rett syndrome</td>
<td>14</td>
</tr>
<tr>
<td>- Mouse model research in Rett syndrome</td>
<td>16</td>
</tr>
<tr>
<td>Discussion</td>
<td>18</td>
</tr>
<tr>
<td>References</td>
<td>20</td>
</tr>
<tr>
<td>Guidelines for contributions for authors (Literature review only)</td>
<td>33</td>
</tr>
<tr>
<td><strong>Article 2: Longitudinal video analysis of gross motor abilities in girls and women with Rett syndrome</strong></td>
<td>39</td>
</tr>
<tr>
<td>Abstract</td>
<td>39</td>
</tr>
<tr>
<td>Introduction</td>
<td>40</td>
</tr>
<tr>
<td>Methods</td>
<td>41</td>
</tr>
</tbody>
</table>
• Data coding ................................................................. 42
• Data analysis ............................................................. 43

Results

• Cases ....................................................................... 44
• Description of motor items ......................................... 44
• General and complex gross motor skills factor scores ...... 44
• Relationships between predictors of gross motor profile score ...... 45

Discussion ................................................................. 45

References ................................................................. 52

Figure 1 ................................................................. 58
Figure 2 ................................................................. 59
Figure 3 ................................................................. 60
Table 1 ................................................................. 61
Table 2 ................................................................. 62
Table 3 ................................................................. 63

Guidelines for contributions for authors (Research report only) .... 64

Appendices .............................................................. 75

Appendix A: Coding Form

Appendix B: Ethics Approval
Gross Motor Abilities and Interventions in Girls and Women with Rett syndrome: A

Literature Review

Kitty-Rose Foley
Gross Motor Abilities and Interventions in Girls and Women with Rett syndrome: A Literature Review

Abstract

Objective: To explore research relevant to an understanding of gross motor abilities and highlight possible directions for gross motor intervention in girls and women with Rett syndrome. A secondary objective was to describe mouse model research which has the potential to add to an understanding of gross motor abilities in this population.

Methods: Electronic searches of five databases, manual searches of an external resource library and manual searches of reference lists were undertaken. The key words imputed during these searches included; mobility, Rett syndrome, functioning, mouse model, therapy and intervention. Search terms were truncated, exploded and adjusted to achieve optimum results. A narrative review was possible.

Results: The searches of the literature yielded research which will be discussed under the headings; phenotype-genotype correlations, gross motor functioning, therapy interventions, involving both gross motor interventions in girls and women with Rett syndrome and mouse model research. The research found that most girls/women with Rett syndrome can sit independently, approximately half can walk and many have difficulties with transitional movements. More complex gross motor skills, such as transitions, walking on a slope and stepping over an obstacle, have been highlighted as especially difficult for this population. Video analysis is an emerging methodology in this area and has the potential to provide better observational data, to measure change, investigate gross motor abilities and evaluate the effectiveness of gross motor interventions. Mouse model research has investigated environmental enrichment as a treatment paradigm resulting in amelioration of gross motor deterioration. Similarly, increasing the expression of BDNF in mice with MeCP2 mutants has resulted in reduced locomotor deficit.

Conclusion: Further longitudinal and cross-sectional studies with rigorous design and larger sample sizes are required in order to guide therapeutic gross motor intervention in girls and women with Rett syndrome.

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Dr Jenny Downs
Dr Sonya Girdler

Submitted: 18th September, 2009
GROSS MOTOR ABILITIES AND INTERVENTIONS IN GIRLS AND WOMEN WITH RETT SYNDROME: A LITERATURE REVIEW

Introduction

Rett syndrome is a rare neurological condition with a prevalence ranging from 1 in 10,000 to 1:20,000 females (Lauvrick et al., 2006; Kozinetz et al., 1993). Rett syndrome severely impacts on the physical and intellectual functioning of an individual yet little is known about the rate of regression and other influencing factors. The disorder is characterised by apparently normal early development followed by neurological regression and developmental arrest between six and 36 months (Hagberg, Hanefeld, Percy, & Skjeldal, 2002). Clinical presentation varies but includes deceleration of head growth, cognitive impairment, loss of hand skills, severely impaired expressive and receptive language, the development of stereotypic hand movements, and gradual decrease in acquired gross motor abilities including gait dysfunction (Hagberg, Aicardi, Dias & Ramos, 1983; Hagberg, 2002; Percy & Lane, 2005).

Four stages have been described reflecting the temporal progression of phenotypic characteristics of Rett syndrome (Hagberg & Witt Engerstrom, 1986). The first stage occurs between six and eighteen months of age. During this autistic stage, the child presents with hypotonia and is unlikely to have learnt to crawl (Bashina, Simashkova, Grachev, & Gorbachevskaya, 2002; Hagberg & Witt Engerstrom, 1986). The second stage, or the regression stage occurs between the age of one and four years. It is characterised by obvious loss of acquired abilities, clumsy or apraxic gait, yet gross motor ability, as a whole, is broadly preserved (Hagberg & Witt Engerstrom, 1986).
In the third stage, the pseudostationary phase, the disease process stabilises and for up to several years. Jerky truncal ataxia is prominent, but overall gross motor function can vary between individuals. The fourth stage, or the late motor deterioration phase, is characterised by decreasing mobility, increasing lower motor neurone signs (scoliosis and trophic foot disturbances), and muscle weakness along with marked spastic rigidity (Hagberg & Witt Engerstrom, 1986: Bashina, Simashkova, Grachev, & Gorbachevskaya, 2002).

The recent finding of mutations in the gene \((MECP2)\) encoding X-linked methyl-CpG-binding protein 2 \((MeCP2)\) as the cause of Rett syndrome has lead to genetic diagnostic testing and increased clinician knowledge allowing early and more efficient diagnosis (Amir et al., 1999; Laurvick et al., 2006). Mutations in the gene \(MECP2\) are found in between 75 to 95% of cases of Rett syndrome (Zoghbi, 2005; Schanen, et al. 2004; Neul, 2008; Amir, Sutton & Van de Veyver, 2005; Hardwick et al., 2007). A number of studies have begun to investigate the relationship between the genetic foundation and specific phenotypic characteristics of girls and women with Rett syndrome. Phenotypic characteristics such as mobility (Downs et al., 2008a; Cass et al., 2003), functional hand use (Downs et al., 2009b), communication (Bebbington et al., 2008), morbidity (Jian et al., 2005), fracture incidence (Downs et al., 2008b), seizure onset (Jian et al., 2006), and over all severity (Bebbington et al., 2008; Charman et al., 2005; Cheadle et al., 2006; Colvin et al., 2003; Colvin et al., 2004; Huppke, Held, Laccone & Hanefeld, 2003) have been investigated, yet many of these studies involve small numbers for each of the common mutations, resulting in difficulties drawing accurate conclusions.
In the absence of a medical cure for Rett syndrome, understanding the progression of this condition is extremely important in providing information to guide therapeutic interventions. The purpose of this literature review was to explore research relevant to an understanding of gross motor abilities and highlight potentially effective gross motor intervention with girls and women with Rett syndrome. A secondary purpose was to describe mouse model research which has the potential to add to an understanding of gross motor abilities in this population.

Methods
To locate the literature relevant to the purpose of this review the databases CINAHL (1982-2009), Medline (1966-2009), ProQuest 5000 International (1938-2009), PsychINFO (1920-2009) and ISI Web of Science (1992-2009) were searched from its earliest records to most recent. The key words imputed during the search included; mobility, Rett syndrome, functioning, mouse model, therapy and intervention. These were truncated, exploded and adjusted to achieve optimum results. Manual searches of an external resource library at the Telethon Institute for Child Health Research was also undertaken. In addition, the reference lists of all relevant articles were manually searched to identify further studies.

A priori criteria for inclusion of studies were applied to identified abstracts then full text articles. Studies were included in the review if the majority of participants were girls/women with Rett syndrome. No minimal or maximum age limit was set. Studies were included if a research method, either quantitative or qualitative, was stated. Outcomes of interest were domains related to gross motor functioning. Conference proceedings, expert opinion reports and research published in a language other than
Gross Motor Ability in Rett syndrome

English were excluded from this review. Articles which met the inclusion criteria were individually analysed, summarised and judged for relevance using the criteria stated.

Results

The literature identified in this search is examined in two parts. Descriptive findings from the literature involving phenotype-genotype relationships, gross motor functioning, scoliosis, and early development in Rett syndrome; and intervention research including gross motor interventions in Rett syndrome and mouse model studies.

Phenotype-Genotype Correlations in Relation to Mobility

Understanding the relationship between phenotype and genotype in Rett syndrome provides practical information to guide therapeutic interventions, design clinical trials and will eventually assist in further understanding of the molecular nature of the MeCP2 protein (Neul, 2008). A number of recent studies have begun to examine this relationship (Bebbington et al., 2008; Colvin et al., 2004; Nuel, 2008; Zhang & Minassian, 2008; Leonard et al., 2005; Archer et al., 2007). A considerable body of research has reported that girls/women with mutation p.R133C and C-terminal deletions experience milder phenotypes (Bebbington et al., 2008; Charman et al., 2005; Colvin et al., 2004; Hoffbuhr et al., 2001; Huppke et al., 2002; Neul, 2008; Smeets et al., 2003). In contrast, girls/women with p.R270X, p.R168X and p.R255X mutations have been found to experience more severe phenotypes (Bebbington et al., 2008; Colvin et al., 2004; Neul, 2008; Smeets et al., 2003).
Girls and women with mutation p.R133C, truncating nonsense mutation p.R294X or C-terminal truncation mutations are significantly more likely to walk, have purposeful hand use and some speech, than those with p.R168X mutation or with large deletions (Neul, 2008). Girls/women with mutation p.R168X were reported to present with an especially severe phenotype in relation to hand function, walking ability, speech, and complex gross motor functions (Downs et al., 2009b; Neul, 2008; Downs et al., 2008a; Colvin et al., 2004). There have been contrasting reports for girls and women with mutation p.R133C. A number of studies have highlighted that girls/women with this mutation present with a milder phenotype (Bebbington et al., 2008; Charman et al., 2005; Colvin et al., 2004; Leonard et al., 2003) however, Schanen and colleagues (2004) did not agree, rather concluding that girls/women with mutation R306C present with the mildest phenotypical characteristics. This difference is likely to be due to their comparatively small sample size (n=85 compared with n=272 in the study by Bebbington and colleagues, 2008), which reduces the power of their findings (Schanen et al., 2004).

Nonsense mutation p.R270X has been identified as resulting in one of the most severe phenotypes in Rett syndrome (Bebbington et al., 2008; Colvin et al., 2004; Charman et al., 2005), and is associated with an increased mortality rate (Jian et al., 2005). Girls and women with mutation p.R270X have been reported to have poorer motor and functional abilities and than those with other mutations (Colvin et al., 2004). They are also more likely to lose skills in motor function, hand use and social interaction earlier (Colvin et al., 2004). Severe restrictions in motor ability are evident as early as ten months for girls and women with a p.R270X mutation. However, those with p.R306C and p.R294X mutations have been found to have milder restrictions in gross
motor ability than those with mutation p.R270X (Leonard et al., 2005; Schanen et al., 2004).

Relationships between genotype and a variety of other phenotypic features of Rett syndrome have been described in the literature. A protective effect against the development of scoliosis has been reported in girls/women with MECP2 mutation p.R294X (Ager et al., 2006). Girls/women with mutation p.R255X have been found to have an increased risk of developing seizures at an earlier age (Jian et al., 2006). Risk of fracture in girls and women with Rett syndrome is four times greater than that of the general population and this risk was specifically increased in girls and women with the p.R270X and p.R168X mutations (Downs et al., 2008b). Collectively, these findings are useful in guiding therapeutic interventions and educating parents and care-givers, yet further research and clarification of the genotype phenotype relationship will provide increased understanding and an improved quality of care.

The study into the relationship between phenotype and genotype has produced variations in findings. Early studies attempted to group mutations in order to increase power, yet may have combined mutations with directly opposing characteristics (such as p.R294X and p.R270X, both nonsense mutations) (Louise et al., 2009). This could have resulted in a nullifying of the results leading to a loss of effect (Louise et al., 2009). The variations in findings between studies may also be attributed to the small sample sizes, and the use of different measures of both phenotype and genotype (Charman et al., 2005).
Gross Motor Functioning

Limitation in gross motor ability is a key diagnostic criterion in Rett syndrome and these girls and women experience a range of difficulties (The Rett Syndrome Diagnostic Criteria Workgroup, 1988; Hagberg, Hanefeld, Percy & Skjeldal, 2002). Neurological signs range from initial hypotonia and flaccidity to spasticity in later childhood. A girl or woman with Rett syndrome may also present with apraxia, balance disturbances, spatial disorientation, ataxia, tremors, rigidity and dystonia (Hagberg, 2002). Joint contractures and scoliosis can also contribute to a decline of motor function (Hagberg & Witt-Engerstrom, 1990). Research into gross motor regression in Rett syndrome is limited, however a number of studies have begun to investigate mobility in girls/women with Rett syndrome (Downs et al., 2008a; Temudo et al., 2008; Leonard et al., 2005; Cass et al., 2003).

Gait of girls and women with Rett syndrome has been described as rigid, lacking coordinated movements of upper extremities, and wide-based with hyperextension of the legs (Nomura & Segawa 1992; Temudo et al., 2008). Although 50 to 80% of girls and women with Rett syndrome achieve mobility in early childhood, longitudinal studies suggest that over 25% of these will eventually lose the ability to walk (Larsson, Lindstrom & Witt-Engerstrom, 2005; Temudo et al., 2008). Complex tasks including transitional movements, such as sit to stand, stand to sit, moving from floor to stand, and bending to touch the floor have been found to be especially difficult for girls and women with Rett syndrome (Downs et al., 2008a; Larsson, Lindstrom, & Witt-Engerstrom, 2005; Cass et al., 2003). Difficulties with these movements may be due to dyspraxia as well as poor muscle tone, co-ordination and balance (Hagberg, 2002; Downs et al., 2008a). Interestingly, Downs and colleagues (2008a), reported that few
Gross Motor Ability in Rett syndrome

girls/women could walk on a slope, step over an obstacle or run, skills which require greater planning, balance and co-ordination. This could be interpreted as dyspraxia becoming more evident with increasingly complex motor tasks. Sitting balance has been highlighted as a strength for girls/women with Rett syndrome as most girls in this study were able to sit (Downs et al., 2008a). Further research into the temporal progression, regression and stagnation of gross motor abilities is required to provide a clearer clinical picture of Rett syndrome.

Early Development

One of the criteria for the diagnosis of Rett syndrome is a normal pre/perinatal period lasting until six to thirty six months (Hagberg, Hanefeld, Percy & Skjeldal, 2002). However, a number of recent studies have suggested that signs of Rett syndrome may be present prior to this time (Leonard et al., 2005; Temudo, Maciel, & Sequeiros, 2007; Larsson, Lindstrom & Witt Engerstrom, 2005; Burford, Kerr & MacLeod, 2003; Trevarthen, & Daniel, 2005; Einspieler, Kerr, & Prechtl, 2005; Segawa, 2005).

Eighty percent (n= 178) of families of children with Rett syndrome from a Swedish study (Larsson, Lindstrom & Witt Engerstrom, 2005), reported that they suspected early that something was wrong with their daughters development. It has also been reported that health professionals are able to recognise signs of developmental deviation in early home videos of infants who later presented with classic Rett syndrome (Burford, Kerr & MacLeod, 2003). These findings suggest that the experienced eye has noteworthy advantages over the clinical test in recognising and diagnosing Rett syndrome at a young age (Burford, Kerr & MacLeod, 2003).
A relationship between patterns of abnormal early development and genotype has been found in girls and women with Rett syndrome indicating developmental delay in early life (Leonard et al., 2005; Larsson, Lindstrom & Witt Engerstrom, 2005). During the pre-regression period a number of symptoms have been reported including, early hypotonia (Nomura & Segawa, 1990), motor problems (Burford, Kerr & MacLeod, 2003), placidity and peri-natal difficulties requiring admission to hospital (Leonard et al., 2005; Leonard & Bower, 1998). The MECP2 mutations p.R255X and p.R270X have been linked with particularly profound disability in early childhood (Leonard et al., 2005). Understanding early development in Rett syndrome is important in efficient, timely diagnosis leading to the possibility of early intervention (Leonard et al., 2005).

Scoliosis

Scoliosis is the most common orthopaedic condition in Rett syndrome (Bassett & Tolo, 1990; McClure, Battaglia & McClure, 1998) and can negatively impact on quality of life and health as it can cause pain, loss of sitting balance, regression of walking skills, and progressive restrictive lung disease (Berven & Bradford, 2002). An Australian population-based study (n= 242) found, the median age of onset of scoliosis was nearly 10 years with three quarters of girls/women developing scoliosis by the age of 13 years (Ager et al., 2006). The strong relationship between gross motor abilities and scoliosis was highlighted in this study with girls/women who were the least mobile at ten months, or who never walked, being more likely to develop scoliosis at a younger age (Ager et al., 2006). Another study by Halbach and colleagues, (2008) involving 53 Dutch participants with Rett syndrome over the age of 16 years reported a prevalence of scoliosis of 90%, highlighting the higher
prevalence of scoliosis in older subjects. Many girls and women with Rett syndrome who develop a scoliosis are subsequently treated with spinal surgery (Larsson et al., 2009; Halbach et al., 2008). Post surgery, girls/women with Rett syndrome have been reported to demonstrate an overall improvement in well-being, an improved sitting posture and better breathing (Larsson et al., 2009; Downs et al., 2009b). However, further research is needed to explore the relationship between the corrective scoliosis surgery and regression of gross motor ability to provide information for the prediction of the syndrome at various ages.

**Outcome Measures and Tools**

Effective, sensitive and appropriate outcome measures and tools are a key component of rigorous research (Law, 2007). Assessing gross motor abilities in girls/women with Rett syndrome is often achieved through clinical observations. An emerging methodology used to analyse gross motor abilities in research, is the use of video analysis in order to provide better observational data, to measure change, investigate gross motor abilities and evaluate the effectiveness of interventions (Downs et al. 2008; Temudo, Maciel, & Sequeiros, 2007; Trevarthen, & Daniel, 2005; Einspieler, Kerr, & Prechtl, 2005; Yasuhara, & Sugiyama, 2001; Burford, Kerr & MacLeod, 2003). Benefits of using video analysis include the ability to capture the activity performance in a familiar environment, decreasing participant stress, and allowing observation of real life function (Fyfe et al., 2007). Video assessment also maximises inclusion allowing participants who live in rural or remote areas to participate in research. Encouraging families to actively engage in research, through collecting video footage, may also have empowering outcomes (Radomske, & Trombly Latham, 2008). An accurate and simple tool to collect data and measure outcomes will aid in
the quality of the research in this field allowing evidence based research to guide therapeutic interventions.

Summary

A number of studies have examined the gross motor abilities of girls and women with Rett syndrome during early development. Relationships between phenotype and genotype and functioning have also begun to be explored. However, there is a paucity of research which examines the progression, regression and stagnation of gross motor abilities throughout the course of the syndrome. At present, there are no longitudinal analyses of gross motor ability in girls and women with Rett syndrome. Understanding in this area has been constrained by small cohorts and the availability of longitudinal data. This review has explored research relevant to an understanding of gross motor abilities in girls/women with Rett syndrome revealing many gaps in the literature. The need for future studies into the progression of gross motor abilities in Rett syndrome has been highlighted, in order to provide information to guide therapeutic interventions.

Therapy Interventions

In the absence of a cure for this disorder, therapeutic intervention is the primary management strategy which may improve quality of life and functioning. The evidence base surrounding intervention strategies for gross motor abilities in Rett syndrome is sparse, with most studies involving very small sample sizes and lacking a control comparison. The following will review the limited amount of evidence in this field.
Aquatic therapy provides an opportunity to improve physiological and psychological achievements as the buoyancy of the water allows independent initiation of movements. There is reduced stress on body parts and joints, and a warm water environment which can reduce muscle tone allowing for more efficient movements (Broach & Datillo, 1996; Hutzler, Chacham, Bergman, & Szeinberg, 1998). A case series described aquatic therapy as a beneficial therapeutic intervention for ten girls and women with Rett syndrome (Lotan & Hadar-Frumer, 2004). However, there was no clear intervention protocol, timeframe or methodology described in this study, yet due to the paucity of research in this area the findings will be discussed (Lotan & Hadar-Frumer, 2004). In this research it was reported that aquatic therapy can play an important role in decreasing muscle rigidity, decreasing oedema and improving flexibility in girls/women with Rett syndrome which can, in turn, potentially lead to an increased quality of life (Lotan & Hadar-Frumer, 2004). Bumin and colleagues (2003) examined the effects of a Halliwick method hydrotherapy program over an eight week period (Bumin, Uyanik, Yilmaz, Kayihan, & Topcu, 2003). Although the study only involved one 11 year old girl, the intervention resulted in a decrease in stereotypical hand movements, increase in hand skills, an improvement in walking balance, and an increase in interactions with her environment (Bumin, Uyanik, Yilmaz, Kayihan, & Topcu, 2003). This research suggests that hydrotherapy has the potential to have positive influences on the functional ability of girls and women with Rett syndrome.

Other physical therapy intervention strategies which have been investigated with girls/women with Rett syndrome include the use of a treadmill intervention, and dual
Interventions of music and physical therapy (Lotan, Isakov and Merrick, 2004; Elefant & Lotan, 2004). It has been suggested that physical therapy could be important in the treatment against scoliosis (Downs 2009b; Rossin, 1997) and assist in the maintenance of the ability to transfer (Hanks, 1990). In a before and after study (n=4), Lotan, Isakov and Merrick, (2004) investigated the feasibility of a physical exercise program with treadmill training. Participants with Rett syndrome who undertook a daily training programme on treadmills for two months showed a significant improvement in physical fitness and functional ability after two months of therapy. The daily training lead to a decrease in heart rate per minute, an indicator of improved fitness. Elefant and Lotan (2004) conducted a case study involving dual intervention of music and physical therapy. Music therapy has been reported as a possible intervention for girls and women with Rett syndrome having the potential to promote and motivate their desire to interact with their environment and assist in developing cognitive, affective, sensory-motor and physical abilities (Hill, 1997; Merker, Bergstrom-Isacsson & Witt Engestrom 2001). The participant in this study, demonstrated improvement in communication choice-making abilities, with the new skills transferring to the classroom and home. However, the explanation of how these outcomes were measured was not clear.

Despite the noted limitations, research in this field has produced promising results implying that gross motor interventions have the ability to make a difference in improving quality of life and functional ability of girls and women with Rett syndrome. Early intervention and preventative management in Rett syndrome have been highlighted as integral in therapy as well as an individualised approach at every age (Halbach et al., 2008). There is a clear need for more rigorous methodologies and
research with larger samples. A greater understanding of the clinical profile of Rett syndrome would support the development of activity programmes that match the physical and physiological potential of girls and women with Rett syndrome (Lotan, Isakov, & Merrick, 2004).

**Mouse Model Research in Rett syndrome**

Animal models provide important opportunities enabling examination of the pathobiology in Rett syndrome (Kondo et al., 2008). Male mice with MeCP2 dysfunction have a phenotype progression similar but more severe than that of girls/women with Rett syndrome (Kondo et al., 2008). Recent studies involving MeCP2 mutant mice have investigated the effects of environmental enrichment (Kondo et al., 2008; Nag et al., 2009), neurometabolites such as choline supplements (Nag, & Berger-Sweeney, 2007; Nag, Mellott, & Berger-Sweeney, 2008) and the role of brain-derived neurotrophic factor (BDNF) (Ward, Kolodny, Nag & Berger-Sweeney, 2009; Bouier et al., 2008; Chang et al., 2006). An important finding has been that neurons are not irreversibly damaged by the absence of MeCP2 during development, as the re-expression of MeCP2 in mutant mice has been observed to suppress mutant phenotype (Guy et al., 2007: Giacometti, Luikenhuis, Beard, & Jaenisch, 2007). This research has provided important insights into the possibilities of treatment in Rett syndrome, implying that an improvement in phenotypic expression may be possible through restoring normal neuronal functionality in postnatal life (Kondo et al., 2008).

Environmental enrichment is a treatment paradigm which has shown beneficial effects on behavioural phenotype and cellular and molecular factors in wild-type and mutant
Gross Motor Ability in Rett syndrome

mice (Rampon et al., 2000; Hockly et al., 2002). Two recent studies investigating the effects of environmental enrichment in a mouse model of Rett syndrome have produced conflicting results (Kondo et al., 2008; Nag et al., 2009). Kondo and colleagues (2008) housed mice with a gross motor deficit in an environment which stimulated sensory, motor and cognitive activity resulting in a reversal of the deficit in motor coordination. However, in contrast to Nag and colleagues, they did not show significant improvements in locomotor activity with environmental enrichment (2009). Nag and colleagues (2009) environmental enrichment involved shavings, tunnels, climbing ladders, and a running wheel which were changed weekly, compared with a control group who were housed in a standard lab cage. There are several influencing factors which may explain the contrasting results between these studies. Kondo and colleagues (2008) incorporated a small sample size (n= 5), used two different strains of mice and the protocol examined only 30 minutes of physical activity a day compared with eight hours investigated by Nag and colleagues (2009). Although there are small inconsistencies between these studies, they both agree that environmental enrichment provides a non-invasive accessible therapy which can be used together with other therapies in order to ameliorate gross motor deterioration in Rett syndrome (Kondo et al., 2008; Nag et al., 2009).

Improvement in motor behaviours and an increased brain volume have been noted as a result of long-lasting improvements in neuronal health in MeCP2 mutant mice (Ward et al., 2009). Treatments of choline supplementation in mice with MeCP2 mutants can cause these long term and possibly permanent improvements in neural integrity (Ward et al., 2009). Nag and Berger-Sweeney (2007) and Nag, Mellott and Berger-Sweeney (2008) conducted research involving similar postnatal choline
supplementation which also highlighted improvements in motor co-ordination, locomotor activity and increases in striatal nerve growth factor level. These findings have significant implications for the future treatment of gross motor abilities of girls and women with Rett syndrome.

BDNF is a neuronal activity-dependent MeCP2 target gene (Bonni et al., 1999). BDNF has the potential to influence onset of seizures, modulate the fetal respiratory rhythm, brain size, locomotor ability, and lifespan in the MeCP2 mutant brain (Bouvier et al., 2008; Chang et al., 2006). Chang and colleagues (2006) reduced the level of BDNF protein in MeCP2 mutant mice and found that this caused an early onset of Rett syndrome features. Subsequently increasing the expression of BDNF resulted in an extended lifespan, reduced locomotor deficit and reversed an electrophysiological deficit. The results of this study suggest therapeutic opportunities involving BDNF, yet also highlights that future studies are required into the molecular basis that underlies its effect on the course of Rett syndrome.

Discussion

This narrative review found that, although limited, there is a growing body of research which explores the gross motor abilities of girls and women with Rett syndrome. Girls/women with mutation p.R270X have been identified as having a severe phenotype resulting in poorer mobility, increased rate of regression in social interaction and hand function and an increased mortality rate. Whereas, girls and women with C-terminal truncations, p.R133C or p.R294X mutations are associated with a milder phenotype. Most girls/women with Rett syndrome can sit independently (Downs et al., 2008a; Cass et al., 2003), many have difficulties performing
transitional movements (Downs et al., 2008a; Cass et al., 2003; Larsson et al., 2005) and approximately half can walk (Downs et al., 2008a; Cass et al., 2003; Huppke et al., 2003). This information has the potential to educate parents and care-givers and provide a broad overview on what to expect in relation to their daughters functioning. However, further longitudinal studies focusing on the progression, regression and/or stagnation of functioning overtime may provide more accurate and useful information for parents and for guiding therapeutic interventions.

There is a clear paucity of research guiding the service delivery of therapy for girls and women with Rett syndrome. The few intervention studies which have been undertaken involve either a single case or small samples which, although useful in identifying areas for potential therapeutic interventions, do not provide a sound evidence base for therapy. However, the research has identified video analysis as a potentially useful, accurate tool for observations and measurement of changes of phenotypic characteristic in girls/women with Rett syndrome (Fyfe et al., 2007). Future studies should aim to provide better quality research through rigorous study design and larger samples to achieve results which may provide a sound evidence base to guide therapeutic interventions.
References


Gross Motor Ability in Rett syndrome


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Longitudinal Video Analysis of Gross Motor Abilities of Girls and Women with Rett Syndrome

Kitty-Rose Foley
Longitudinal Video Analysis of Gross Motor Abilities of Girls and Women with Rett Syndrome

Abstract

**Purpose:** Rett syndrome is a rare neurological disorder often associated with a mutation in the *MECP2* gene. It results in severe physical and intellectual disability with a gradual decrease in acquired gross motor abilities. This study explored changes in gross motor abilities over three years in girls/women with Rett syndrome, recruited from a population-based data base. The relationships between these changes and age and genotype were investigated.

**Method:** Families participating in the Australian Rett Syndrome Database were invited to participate in a video study. Ninety-nine families provided a video in 2004 and 70 of these cases submitted a second video in 2007. Gross motor data for the two time points were scored through the use of an assessment tool based on the Gross Motor Function Measure.

**Results:** The level of general gross motor skills decreased in 58 (82.9%) and increased in 12 (17.1%) cases (mean decrease in z-score 0.50 ± 0.59). The level of complex gross motor skills decreased in 67 (95.7%) and increased in 3 (4.2%) cases (mean decrease in z-score 1.58 ± 1.11). General motor skills declined for cases in each of the four age-groups. Compared to the girls who were younger than 8 years, the decrease in complex motor skills was greater for girls aged 13≤19 years (P=0.021) and women >19 years (P=0.071).

**Conclusion:** Over a 3-year period, there was a small amount of deterioration in general gross motor skills for girls of all ages and a larger deterioration in complex gross motor skills during the teenage years. This detailed understanding of the characteristics of declining gross motor skills in Rett syndrome could contribute to the development of strategies to ameliorate these trends.

Keywords: Mobility, development, functioning, deterioration, phenotype, genotype.

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Submitted: 18th September, 2009
LONGITUDINAL VIDEO ANALYSIS OF GROSS MOTOR ABILITIES OF GIRLS AND WOMEN WITH RETT SYNDROME

Introduction

Rett syndrome is a rare neurological disorder affecting one in 8,500 girls/women in Australia under the age of 15 [1]. In most cases, it is caused by an X-linked dominant mutation of the MECP2 gene, usually resulting in lethality in hemizygous males [2, 3]. Rett syndrome is characterised by severe physical and intellectual disability. Clinical presentation varies but includes deceleration of head growth, cognitive impairment, loss of hand skills, severely impaired expressive and receptive language, the development of stereotypic hand movements and a gradual decrease in acquired gross motor abilities [4, 5]. Gross motor abilities of girls and women with Rett syndrome range considerably; a cross-sectional population-based study showed that approximately half of girls/women with Rett syndrome learned to walk, most could sit independently and many had difficulties with transitional movements [6]. It has been reported that gross motor abilities improve until adolescence and then decline [5]. Recent research in the Australian cohort of girls/women with Rett syndrome has suggested that the level of skill for more complex gross motor skills (such as transferring from floor to standing, picking up an object from the floor and walking on a slope) may be more stable over time although this finding may have been due to a floor effect [6]. This longitudinal study will further explore these changes.

Relationships between gross motor abilities and presence of scoliosis [7] and genotype [8-10] have also begun to be explored. It has been found that girls and women with mutation p.R270X [6, 8, 9] and p.R168X [9, 10] present with a more
severe phenotype in relation to motor abilities, whereas those with p.R133C, p.R294X and C-terminal deletions are more likely to walk and have some purposeful hand-use [10]. Scoliosis is also associated with poorer motor abilities with girls/women who were the least mobile at ten months, or who never walked being more likely to develop scoliosis at a younger age [7]. Although research has begun to draw conclusions about phenotypic and genotypic characteristics in Rett syndrome, there is a clear paucity of research investigating longitudinal changes. The aim of this study was to identify changes in gross motor ability in girls/women with Rett syndrome over three years and investigate the nature of these changes in relation to age and genotype.

Methods

The Australian Rett Syndrome Database is a population-based register of confirmed Rett syndrome cases in Australia [11]. In 2004, families of cases in the Australian Rett Syndrome Database were invited to participate in a video study which resulted in 99 videos being available for cross sectional gross motor profile analysis [6]. In 2007, families were again invited to participate in a follow-up video study (refer to figure 1). Seventy of the 99 cases on whom a video was returned in the 2004 study also had a subsequent video in 2007, allowing for observations at two time points for each of these subjects.

In both 2004 and 2007, the consenting families were sent a filming protocol, demonstration video, blank video, and a parent report checklist [12]. The filming protocol was developed with input from professionals in the relevant areas. The demonstration video which provided a guide for families as a supplement to the
filming protocol, included four girls with Rett syndrome of varying ages and functional abilities. The families were asked to film their daughter's natural everyday tasks in a familiar environment. Activities filmed included elements of self-care, eating and meal times, hand function, gross motor activities and communication. Ethics approval was obtained from the Ethics Committee of the Women’s and Children’s Health Services in Western Australia and written informed consent obtained from the families.

Data Coding

The assessment tool used to evaluate gross motor abilities was developed specifically for this video study [12] and contained specific items from the Gross Motor Function Measure [13] as well as other items relevant to the daily lives of people with a disability. Our gross motor measure assessed items including sitting (on a chair, stool and on the floor), standing (for three, ten and twenty seconds), transfers (sit to stand, stand to sit, floor to stand, and bending to the floor), walking skills (walking ten steps, side-stepping, stepping over an obstacle, turning 180 degree and walking on a slope), and running [6]. A score, reflecting the girl’s or woman’s best ability, was allocated to each item based on the level of assistance required which ranged from no assistance, mild assistance, moderate assistance and maximal assistance. Training of the researcher responsible for coding was conducted by an expert to ensure inter-rater reliability in coding. Several training sessions, with 2004 videos which were not part of the current study, were held, to practise coding. Approximately twenty-five videos were then coded independently by the trainee and checked with previous codes. Where discrepancies were evident, the trainee and expert viewed and discussed the data together. KAPPA calculations were used to evaluate the inter-rater reliability of
the two researchers, which resulted in a score of >0.80 for all items. Where possible, missing video data was added from information in the parent report checklists.

Previous data analysis identified two subscales [6]; ‘General Gross Motor Skills’ representing the more basic motor tasks describing sitting, standing, walking, side stepping, turning 180 degrees and transferring from sit to stand with a Cronbachs $\alpha$ coefficient of 0.96. Other skills, such as moving from floor to standing, bending to the floor, stepping over an obstacle, walking on a slope, and running loaded strongly on factor two, ‘Complex Gross Motor Skills’ (Cronbachs $\alpha$ coefficient = 0.89) [6]. These factors allowed for further analysis and investigation of the relationship of gross motor abilities with other variables.

Data Analysis

Fifteen mobility items were coded from the best ability viewed on the videos and information from the parent report checklists for each individual. Additional missing data were imputed through regression. Variables were constructed which represented the change in status between 2004 and 2007 for each mobility item. The code for each item was then used to calculate the two subscale scores, expressed as z-scores and the change in z-score was calculated. Linear regression models were used to analyse the relationship between change in mobility scores, age group, and genotype. All analyses were undertaken using Stata 10 [14].
Results

Cases
Age in 2004 was grouped into four categories; ≤8 years (n=19), 8 ≤13 years (n=12), 13 ≤ 19 years (n=21) and 19 years or older (n=18). MECP2 mutations had been confirmed in 51 (72.9%) of the 70 cases in whom mutation testing had been completed. The most common mutations were p.R270X (n=7), C-terminal truncations (n=6), p.R168X (n=5), p.R294X (n=5), p.R306C (n=4), p.R133C (n=4), p.T158M (n=4), and large deletions (n=4).

Description of motor items
In 2004, just under half of the sample could walk (n=30, 45%), over half could sit on a chair independently (n=44, 63%), and a smaller number (n=14, 23%) could perform sit to stand transfers. In 2007, slightly fewer girls/women could walk (n=28, 42%) and approximately half of those who could transfer from sitting to standing in 2004 had lost this ability (n=8 able to transfer in 2007 compared with n=14 in 2004). The number of cases who could perform each item declined from 2004 to 2007 in every skill, except for the item measuring sitting on a chair with a back, where seven cases improved while only five declined (table 1).

General and Complex gross motor skills factor scores
In 58 cases ‘General Gross Motor Skills’ scores declined over the three year period, while 12 improved slightly resulting in a mean decrease in z-score of 0.51±0.59. In relation to ‘Complex Gross Motor Skills’, skill level declined in 67 (95.7%) cases and only three girls/women improved (mean decrease in z-score 1.58±1.11). A trend
towards deterioration in both general and complex gross motor skills was apparent over the 3 year period.

Relationship between predictors of motor profile score

All genotype mutation groups appeared to deteriorate in complex and general gross motor skills except for girls and women with p.R168X mutation whose general gross motor skills slightly improved (P=0.011) in comparison with those with C-terminal truncations. Girls/women with C-terminal truncations deteriorated the most from 2004 to 2007 (mean 0.85±0.66) in general gross motor skills, followed by girls and women with mutation p.R270X (P=0.403) where girls/women with C-terminal deletions were the baseline (figures 2 and 3).

Gross motor abilities in 2007 were predicted by functioning in 2004 scores in both general (P<0.001) and complex skills (P<0.001). Compared with those who were aged 8 years and younger, the decrease in complex gross motor skills was greater for those girls/women who were 13≤19 years (P=0.021) and over 19 years of age (P=0.071) (table 2). A trend between age group and deterioration in general gross motor skills was apparent with the 13≤19-year-old girls/women deteriorating the most when compared with the youngest age group (P=0.173) (refer to table 3).

Discussion

Previous research has suggested that gross motor skills decline over time in Rett syndrome [5, 6, 15], yet the rate of deterioration and variability between genotype and age groups was, until now, largely unknown. This study provides longitudinal evidence of a deterioration of gross motor abilities in a population-based Australian
Gross Motor Ability in Rett syndrome

cohort, through the use of a video assessment tool. The ability to transfer from sit to stand was found to decrease the most, followed by the skills transferring from floor to stand, stool sitting, sitting on the floor and standing. Due to the heavier weightings of the items loading on the complex gross motor skills factor [6], overall findings showed a marked deterioration of complex gross motor skills in comparison with general gross motor skills.

Four stages of Rett syndrome have been described which highlight the deterioration of gross motor skills during the fourth stage, or the ‘late motor deterioration phase’ [4]. The findings in this study support the theory of these stages, as the girls and women in the older age groups, 13≤19 years and >19 years, showed the most deterioration of complex skills. A trend towards deterioration of general gross motor skills for all age groups was also evident. Girls/women with a C-terminal deletion or p.R270X mutation showed the most deterioration in general motor skills whereas those with a p.R133C, p.R255X or p.R306C mutation showed the most deterioration of complex gross motor skills.

Dyspraxia is common in Rett syndrome [5] and can result in difficulties in initiating, planning, co-ordinating and performing a skill [16]. In this study complex gross motor skills and general gross motor skills deteriorated for all age groups. Previous research presented the idea that girls/women may be more likely to retain complex gross motor skills in comparison with general gross motor skills [6]. As suggested by Downs and colleagues [6], it is likely that dyspraxia is more evident during complex tasks, which may play a role in the poor level of skill shown in these tasks. Other factors such as growth, muscle weakness, other medical co-morbidities and/or opportunities to
practise in daily life may explain the decline in complex skills in comparison with general skills in this study.

Gait of girls/women with Rett syndrome has been described as rigid lacking coordinated movements of upper extremities, ataxic and wide-based with hyperextended legs [17, 18]. Toe-walking and shuffling are also seen as typical gait patterns in this population [5, 6]. Consistent with samples in other studies [6, 15, 19], we found that half of cases in our sample could walk in 2004, with only slight deterioration after three years. A smaller proportion of girls and women were able to stand with no assistance when compared to those who could walk. Half of those who could stand, could only stand for three seconds, which may indicate that they are likely to shuffle or toe walk. Larsson and Witt-Engerstrom [20] reported in a single-case report, that it was possible for a woman with Rett syndrome to regain the ability to walk, even after 15 months in a wheelchair. The strategies they used included consideration of dyspraxia, memory of earlier function, and the importance of repetition. The inability to stand has many functional implications such as increased difficulties with dressing and transfers. Future interventions should target the maintenance of this skill to decrease the burden of care on parents and care-givers and possible delay the onset of complications such as joint contractures and deformities.

Girls and women with Rett syndrome have been observed to have difficulties with transitional movements, including sit to stand, floor to stand and bending to the floor and returning to standing [6, 15]. Performing transitional movements requires motor planning, balance and co-ordination and can be effected by dyspraxia and poor muscles tone, often present in Rett syndrome [5, 6]. Half of those who could transfer
independently from sit to stand in 2004 had lost this ability in 2007 with 36.8% needing maximal assistance to complete the skill. Due to the important burden this is likely to place on families and carers, maintenance of transitional movements could be an area for future intervention, as suggested by previous research [6, 20, 21].

Sitting was highlighted as a strength in this Australian cohort in 2004 [6]. We found that the ability to stool sit declined in 22.9% of our sample. This item represented one of the largest decreases in skill level, highlighting the importance of therapy targeting maintenance of core strength and postural control.

Complex gross motor skills for girls/women who were 13≤19 years of age decreased significantly in this study, and a marked decrease for those over 19 years of age was evident. Cass and colleagues [15], reported a deterioration of transitional skills into adulthood yet they also reported that 50% of their cohort remained mobile. However, this data was not longitudinal or population-based and may be, in part, due to a survivor bias towards adult women who were still walking. Our finding, pertaining to girls/women over the age of 13 years, highlights that this may be a time of acute deterioration of skills. It may therefore be appropriate to target therapy towards maintenance of these complex gross motor skills at this time to help maintain functioning and maximise skill level. Continuation of therapy into adult years, a time when therapy usually decreases [22], may also play an important role in maintenance of gross motor skills for this population.

Analysis of genotype relationships proved difficult due to power limitations. Despite this, several interesting findings emerged, highlighting the need for future
investigation. Girls and women with mutation p.R168X have been found to present with a more severe phenotype in relation to hand function, walking ability, speech and complex gross motor functions [6, 10, 23] although this may have been partly due to a bias towards survivors [6, 10]. However, in some research p.R168X has not consistently been reported as one of the most severe mutations [8, 24-26]. Other research suggested that those with this mutation may present with a varying phenotype of clinical severity, possibly due to the role of other epigenetic influences, such as X-inactivation [27] and the BDNF polymorphism [28]. In our study, girls and women with mutation p.R168X complex motor skills declined, yet their general skills improved mildly, which further confirms this broad expression of phenotype.

Disorder profiles, which include the progress over time, of recurrent MECP2 mutations are starting to be described [29]. Girls and women with C-terminal deletions were reported as becoming impaired in walking and being slower and more passive in general motor performance with advancing age [30]. In contrast, their simple communicative and cognitive abilities were said to improve. Hagberg and colleagues [31] also presented a case-study of a woman with a C-terminal deletion who showed this decline of neuromotor ability. Consistent with this research, we found the largest deterioration of general gross motor skills from 2004 to 2007 occurred in girls and women with C-terminal truncations.

Girls and women with p.R270X mutations may present with a classic Rett disorder profile with an early clinical diagnosis and subsequent rapidly increasing clinical severity with advancing age [29]. Our sample of girls/women with p.R270X mutations, although limited by sample size (partly account of increased mortality
Gross Motor Ability in Rett syndrome

Gross Motor Ability in Rett syndrome [32]), confirms this, as they showed a marked deterioration of general gross motor abilities compared with other genotypes. Other studies have also found girls/women with p.R270X mutations to present with a more severe phenotype [8, 9, 33]. This finding is consistent with the literature and provides important information for parents and care-givers concerning the likely progression of their daughters’ gross motor abilities.

In addition to the power limitations for genotype analyses, interpreting the rate of deterioration of general and complex skills also proved difficult. This was due to the fact that losing a complex skill had more statistical weight than losing a general skill due to clumping of complex skills. For instance, girls and women who could perform one complex task (eg. running) could often perform the other complex tasks (eg. walking on a slope and bend to touch the floor). The fact that the mean z-score for decrease in complex gross motor skills was much lower than the score for general skills is not necessarily reflective of a larger decline of ability. Overall, the original factor analysis provides some evidence of declining skill when the person is measured twice using the same system. A bias towards survivors was also evident in this study due to the longitudinal nature of the design.

A key element for future research to consider is the development of an assessment tool to be used to evaluate therapy. As this study and many others have presented [6, 15, 20], an increase in therapy targeting areas such as, maintenance of transitions, sitting ability and maintenance of complex skills during adolescence, may result in an increase in quality of life and a reduction of the burden on families and care-givers. This study presents important information showing a longitudinal picture of gross
motor abilities providing an overview of the natural regression in Rett syndrome. However, the development of an appropriate measure to assess the success of therapy should be an investigated in future research.

This longitudinal population-based study provides interesting insights into the progression of general and complex gross motor abilities in Rett syndrome. We have presented key information for clinicians and families regarding possible skill areas that may decline at various ages. This information can be used to guide therapeutic intervention and develop achievable goals and outcomes. Investigating the phenotype-genotype relationship has continued to prove difficult due to limited sizes of genotype groups yet this study presents information which further assists in the clarification of these relationships. These data will continue to be expanded and used for further longitudinal studies over a more extended time period to provide a more thorough clinical picture of the progression, stagnation and regression of gross motor abilities in Rett syndrome.
References


Figure 1: Flow chart of cross-sectional and longitudinal video studies.

- Invitations and consent forms sent to all cases in the ARSD in 2004 and 2007
- Signed consent forms returned
  - Video package and questionnaires sent
  - 99 videos and questionnaires returned in 2004
  - 99 cases video data coded and analysed
  - Cross-sectional Gross motor profile of 99 cases (Downs et al., 2008)
  - Comparison of 70 cases from 2004 to 2007 in this study
  - 156 videos and questionnaires returned in 2007
    - 70 cases also returned video in 2004
    - 70 cases video data coded and analysed in this study
Figure 2: Mean ± 95%CI z-score changes from 2004 to 2007 in General gross motor skills by genotype.
Figure 3: Mean ± 95%CI z-score changes from 2004 to 2007 in Complex gross motor skills by genotype.
Table 1: Change in status of individual items between 2004 and 2007.

<table>
<thead>
<tr>
<th>Item (n)</th>
<th>Improved level of skill n (%)</th>
<th>Maintained level of skill n (%)</th>
<th>Decreased level of skill n (%)</th>
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<tr>
<td>Sitting</td>
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<tr>
<td>Sitting on the floor (48)</td>
<td>8 (16.7%)</td>
<td>29 (60.4%)</td>
<td>11 (22.9%)</td>
</tr>
<tr>
<td>Sitting on a chair with back (70)</td>
<td>7 (10.0%)</td>
<td>58 (82.9%)</td>
<td>5 (7.14%)</td>
</tr>
<tr>
<td>Sitting on a stool (52)</td>
<td>4 (7.7%)</td>
<td>36 (69.2%)</td>
<td>12 (23.1%)</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 seconds (65)</td>
<td>9 (13.8%)</td>
<td>46 (70.8%)</td>
<td>10 (15.4%)</td>
</tr>
<tr>
<td>10 seconds (59)</td>
<td>8 (13.6%)</td>
<td>37 (62.7%)</td>
<td>14 (23.7%)</td>
</tr>
<tr>
<td>20 seconds (51)</td>
<td>4 (7.8%)</td>
<td>35 (68.6%)</td>
<td>12 (23.5%)</td>
</tr>
<tr>
<td>Transfers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sit to stand (60)</td>
<td>5 (8.3%)</td>
<td>38 (63.3%)</td>
<td>17 (28.3%)</td>
</tr>
<tr>
<td>Floor to stand (43)</td>
<td>2 (4.7%)</td>
<td>31 (72.1%)</td>
<td>10 (23.3%)</td>
</tr>
<tr>
<td>Bend to touch floor (31)</td>
<td>-</td>
<td>30 (96.8%)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 steps forward (63)</td>
<td>1 (1.6%)</td>
<td>55 (87.3%)</td>
<td>7 (11.1%)</td>
</tr>
<tr>
<td>Side-step (42)</td>
<td>2 (4.8%)</td>
<td>38 (90.5%)</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Turn 180 degrees (52)</td>
<td>3 (5.8%)</td>
<td>43 (82.7%)</td>
<td>6 (11.5%)</td>
</tr>
<tr>
<td>Step over obstacle (36)</td>
<td>2 (5.6%)</td>
<td>29 (80.6%)</td>
<td>5 (13.9%)</td>
</tr>
<tr>
<td>Walk on slope (35)</td>
<td>3 (8.6%)</td>
<td>28 (80.0%)</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>Run (42)</td>
<td>-</td>
<td>40 (95.2%)</td>
<td>2 (4.8%)</td>
</tr>
</tbody>
</table>
Table 2: Regression analysis of the influence of age group and mutation type on the change in Complex gross motor abilities from 2004 to 2007.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category (n)</th>
<th>All cases (n=70)</th>
<th>Cases with known pathogenic mutations (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>P value</td>
<td>Mean difference (95% CI)</td>
</tr>
<tr>
<td>Common mutation</td>
<td>C-terminal truncating (6)</td>
<td>-1.30 (-2.12, -0.48)</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>R133C (4)</td>
<td>-2.52 (-3.52, -1.51)</td>
<td>0.066</td>
</tr>
<tr>
<td></td>
<td>R168X (5)</td>
<td>-2.46 (-3.60, -1.56)</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>R270X (7)</td>
<td>-1.31 (-2.07, -0.55)</td>
<td>0.986</td>
</tr>
<tr>
<td></td>
<td>R294X (5)</td>
<td>-2.24 (-3.14, -1.34)</td>
<td>0.129</td>
</tr>
<tr>
<td></td>
<td>R306C (4)</td>
<td>-2.55 (-3.56, -1.54)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>T158M (4)</td>
<td>-2.39 (-3.40, -1.39)</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td>Large deletions (4)</td>
<td>-1.20 (-2.20, -1.20)</td>
<td>0.875</td>
</tr>
<tr>
<td></td>
<td>Other (8)</td>
<td>-0.95 (-1.66, -0.24)</td>
<td>0.517</td>
</tr>
<tr>
<td></td>
<td>No mutation (17)</td>
<td>-1.12 (-1.61, -0.63)</td>
<td>0.705</td>
</tr>
<tr>
<td>Age-group (years)</td>
<td>≤ 8 (19)</td>
<td>-1.97 (-2.45, -1.48)</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>8 ≤ 13 (12)</td>
<td>-2.06 (-2.67, -1.45)</td>
<td>0.816</td>
</tr>
<tr>
<td></td>
<td>13 ≤ 19 (21)</td>
<td>-1.17 (-1.64, -0.71)</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>≥ 19 (18)</td>
<td>-1.33 (-1.83, -0.83)</td>
<td>0.071</td>
</tr>
</tbody>
</table>
Table 3: Regression analysis of the influence of age group and mutation type on the change in General gross motor abilities from 2004 to 2007.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category (n)</th>
<th>All cases (n=70)</th>
<th>Cases with known pathogenic mutations (n=51)</th>
<th>P value</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Mutation</td>
<td>C-terminal truncating (6)</td>
<td>-0.85 (-1.30, -0.39)</td>
<td>Baseline</td>
<td>Baseline</td>
<td>-0.85 (-1.34, -0.35)</td>
<td>0.092</td>
<td>-0.23 (-0.84, 0.37)</td>
</tr>
<tr>
<td></td>
<td>R133C (4)</td>
<td>-0.23 (-0.79, 0.32)</td>
<td>0.092</td>
<td>0.041</td>
<td>-0.46, 0.53</td>
<td>0.011</td>
<td>0.04 (-0.51, 0.58)</td>
</tr>
<tr>
<td></td>
<td>R168X (5)</td>
<td>0.04 (-0.46, 0.53)</td>
<td>0.092</td>
<td>0.041</td>
<td>-0.46, 0.53</td>
<td>0.011</td>
<td>0.04 (-0.51, 0.58)</td>
</tr>
<tr>
<td></td>
<td>R270X (7)</td>
<td>-0.59 (-1.01, -0.17)</td>
<td>0.403</td>
<td>0.59 (-1.04, -0.13)</td>
<td>0.439</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R294X (5)</td>
<td>-0.22 (-0.71, 0.28)</td>
<td>0.065</td>
<td>-0.22 (-0.76, 0.33)</td>
<td>0.089</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R306C (4)</td>
<td>-0.31 (-0.86, 0.25)</td>
<td>0.137</td>
<td>-0.31 (-0.91, 0.30)</td>
<td>0.169</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T158M (4)</td>
<td>-0.07 (-0.62, 0.49)</td>
<td>0.033</td>
<td>-0.07 (-0.67, 0.54)</td>
<td>0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large deletions (4)</td>
<td>-0.40 (-0.96, 0.16)</td>
<td>0.217</td>
<td>-0.40 (-1.00, 0.21)</td>
<td>0.253</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (8)</td>
<td>-0.60 (-1.00, -0.21)</td>
<td>0.418</td>
<td>-0.60 (-1.03, -0.18)</td>
<td>0.453</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Mutation (17)</td>
<td>-0.70 (-0.97, -0.43)</td>
<td>0.573</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-group (years)</td>
<td>≤ 8 (19)</td>
<td>-0.39 (-0.66, -0.12)</td>
<td>Baseline</td>
<td>Baseline</td>
<td>-0.35 (-0.65, -0.05)</td>
<td>0.954</td>
<td>-0.29 (-0.62, 0.04)</td>
</tr>
<tr>
<td></td>
<td>8 ≤ 13 (12)</td>
<td>-0.61 (-0.95, -0.26)</td>
<td>0.324</td>
<td>-0.63 (-1.07, -0.20)</td>
<td>0.286</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 ≤ 19 (21)</td>
<td>-0.65 (-0.91, -0.39)</td>
<td>0.173</td>
<td>-0.45 (-0.81, -0.10)</td>
<td>0.651</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 19 (18)</td>
<td>-0.40 (-0.68, -0.12)</td>
<td>0.954</td>
<td>-0.29 (-0.62, 0.04)</td>
<td>0.795</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guidelines for Contributions by Authors (Research report only)

Disability & Rehabilitation

Official journal of the International Society of Physical and Rehabilitation Medicine (ISPRM)

Instructions for Authors

Disability and Rehabilitation is an international, multidisciplinary journal which seeks to encourage a better understanding of all aspects of disability, and to promote the rehabilitation process. The journal publishes articles on a range of issues including the severity and magnitude of disability, clinical medicine including gerontology, psychosocial adjustment, social policy issues and vocational and educational training.

Disability and Rehabilitation seeks to encourage a better understanding of all aspects of disablement and to promote the rehabilitation process. New submissions on any aspect of disability and rehabilitation are encouraged.

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Disability and Rehabilitation will be of interest to a wide range of professional groups, including medical practitioners, occupational therapists, physiotherapists, speech and language therapists, clinical psychologists and those involved in nursing, education, ergonomics and engineering.

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All papers submitted to Disability and Rehabilitation should have a 'structured
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**Results** Present the main results.

**Conclusions** State the conclusions that have been drawn and their relevance to the study of disability and rehabilitation.

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When experimental animals are used, state the species, strain, number used, and other pertinent descriptive characteristics.

For human participants or patients, describe their characteristics.

For human participants in a research survey, secure the consent for data and other material - verbatim quotations from interviews, etc. - to be used.

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The registry must be accessible to the public at no charge, be open to all prospective registrants and managed by a not-for-profit organization. For a list of registries that meet all of these requirements, please see the WHO International Clinical Trials Registry Platform (ICTRP) [http://www.who.int/ictrp/en/](http://www.who.int/ictrp/en/). This is in accordance with the guidelines published by the International Committee of Medical Journal Editors (ICMJE). For more information, see ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals [http://www.icmje.org](http://www.icmje.org).

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We welcome figures, but care and attention to these guidelines is essential, as importing graphics packages can often be problematic.

Avoid the use of colour and tints for aesthetic reasons. Figures should be produced as near to the finished size as possible.

All figures must be numbered in the order in which they occur (e.g. figure 1, figure 2 etc.). In multi-part figures, each part should be labelled (e.g. figure 1 (a), figure 1 (b) etc.)

The figure captions must be saved as a separate file with the text and numbered correspondingly.

The filename for the graphic should be descriptive of the graphic e.g. Figure1, Figure2a.

Files should be saved as TIFF (tagged image file format), PostScript or EPS (encapsulated PostScript), containing all the necessary font information and the source file of the application (e.g., CorelDraw/Mac, CorelDraw/PC).

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Some specific points of style for the text of articles, research reports, case studies, reports, essay reviews, and reviews follow:

1. We prefer US to 'American', USA to 'United States', and UK to 'United Kingdom'.
2. We use conservative (British, not US, spelling, i.e. colour not color; behaviour (behavioural) not behavior; [school] programme not program; [he] practises not practices; centre not center; organization not organisation; analyse not analyze, etc.
3. Single 'quotes' are used for quotations rather than double "quotes", unless the 'quote is "within" another quote'.
4. Punctuation should follow the British style, e.g. 'quotes precede punctuation'.
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Full formulae or equations should be displayed, that is, written on a separate line. Horizontal lines are preferable to solidi, for example:

\[ \frac{61 + 5h + q}{3n + 3yz^2} \]

But: \( \frac{a}{b} + \frac{c}{d} + \frac{a}{d} \)

\[ P = (a^2 + b^2)(c^2 + d^2) \]

The solidus is not generally used for units: m/s^{-1} not m/s, but note electrons/s, counts/channel, etc.

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   [Insert table 2 about here]

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Acknowledgements

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Appendices

Appendix A: Coding Form

Appendix B: Ethics Approval