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Growing pains: Twin family study evidence for genetic susceptibility and a genetic relationship with restless legs syndrome

D. Champion[1,2], S. Pathirana[1,2,*], C. Flynn[1,2,*], A. Taylor[1,2], J.L. Hopper[3], S.F. Berkovic[4], T. Jaaniste[1], W. Qiu[1]

1 Department of Anaesthesia and Pain Medicine, Sydney Children's Hospital, Randwick, Australia
2 Faculty of Medicine, University of New South Wales, Sydney, Australia
3 School of Population Health, The University of Melbourne, Australia
4 Department of Medicine, Austin Health, University of Melbourne, Australia

Correspondence
David Champion
E-mail: dchamp@bigpond.net.au

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* Shanthi Pathirana and Carla Flynn are equal second authors.

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Abstract

Background: Growing pains (GP) is a prevalent familial childhood disorder of unknown aetiology. Familial occurrence of GP, and individual and familial association of GP with restless legs syndrome (RLS) has been reported.

Methods: We applied a twin family design to search for evidence of genetic susceptibility to GP, and for a genetic relationship between GP and RLS. The parents of 1843 twin pairs aged 3–16 years were administered a questionnaire, which identified 88 pairs with at least one twin individual fulfilling criteria for GP. Standard questionnaires for history of GP and RLS were completed for these twin pairs, their siblings and parents.

Results: Twenty-five of 34 monozygotic (MZ) pairs were concordant for GP, compared with 12 of the 54 dizygotic (DZ) pairs. The casewise concordance was 0.85 and 0.36 for MZ and DZ pairs, respectively ($p < 0.001$). The lifetime GP prevalence for relatives of twins with GP was 51% for non-twin siblings, 47% for parents. Twenty-three percent of twin individuals with GP met RLS criteria compared with 8% of twin individuals without GP ($p = 0.03$). Of the twins with GP concordance, 19% met RLS criteria compared with 2% of twins with GP discordance ($p = 0.01$). In two MZ pairs, one had GP and the other RLS. The lifetime prevalence of RLS was 40% for mothers, and 24% for fathers and 18% for non-twin siblings.

Conclusion: This first twin family study of GP provides evidence for a genetic aetiology and for a genetic relationship to RLS.

1. Introduction

Growing pains (GP), a benign nocturnal limb pain disorder of childhood, has been reported to have a wide range of prevalence estimates from 3% to 49% (Evans and Scutter, 2004). This variation is likely due to differences in diagnostic criteria, populations, sampling methods and prevalence determination ranging from point to lifetime.

The question 'what is this malady called growing pains?' raised by Naish and Apley in 1951 (Naish and Apley, 1951) has not yet been adequately answered. For this project, we have defined GP according to criteria derived from Peterson (1986), i.e., as a disorder characterized by intermittent, bilateral leg pain occurring late in the day or at night in children who have no abnormal findings on physical examinations and/or imaging and laboratory investigations. GP is an idiopathic functional pain syndrome (Uziel and Hashkes, 2007). Attributions of GP to growth itself (Naish and Apley, 1951), relative hyperactivity and fatigue (Brenning, 1960; Baxter and Dulberg, 1988;

What's already known about this topic?
- Growing pains is known to be familial.
- It has also been associated with restless legs syndrome in individuals who have or have had growing pains and their parents.

What does this study add?
- Applying the twin family design has determined a probability that growing pains is not just familial, but is probably genetically influenced and associated with restless legs syndrome.

Friedland et al., 2005; Evans et al., 2006), anatomical/biomechanical factors (Hawksley, 1939; Evans, 2003) and psychogenic factors (Oberklaid et al., 1997; Paulus et al., 2007) have not been substantiated.

We are unaware of any published clinical genetic studies of GP. In an unpublished community survey of children with GP, we found that 69% of the children had a family history of GP, and that two- and three-generational histories of GP were not uncommon. Frequent family history of GP has been reported by many authors including Brenning (1960), Evans and Scutter (2004) and Pavone et al. (2011). There have also been reports of within-individual and within-family relationships between GP and restless legs syndrome (RLS; Brenning, 1960; Apley, 1976; Bassetti et al., 2001; Walters, 2002; Rajaram et al., 2004; Picchietti and Stevens, 2008; Turkdogan et al., 2011). To our knowledge, there are no publications on twin studies of GP.

The current study involved a twin family design. Under the assumptions of the classic twin model, that monozygotic (MZ) and dizygotic (DZ) twin pairs share to the same extent the non-genetic factors relevant to the trait of interest, we aimed to test the hypothesis that there is a genetic susceptibility to GP. We then tested if the concordance was similar for different types of first-degree relatives (DZ twins, siblings and parents), as would be predicted if a genetic susceptibility explained familial associations. We also sought to determine if there was evidence that this genetic susceptibility to GP was also related to susceptibility to RLS by studying the familial relationships between these traits.

2. Methods

2.1 Recruitment

A total of 1843 unselected families with twins aged 3–16 years were approached through the Australian Twin Registry (ATR). As portrayed in Fig. 1, the ATR applied the survey inclusion criteria to the Twin Registry database, and made a random selection of twin families who had not been approached in the previous 6 months. The parents were mailed a screening questionnaire that asked 'Have one or both of your twins ever experienced limb pains, especially in the legs and

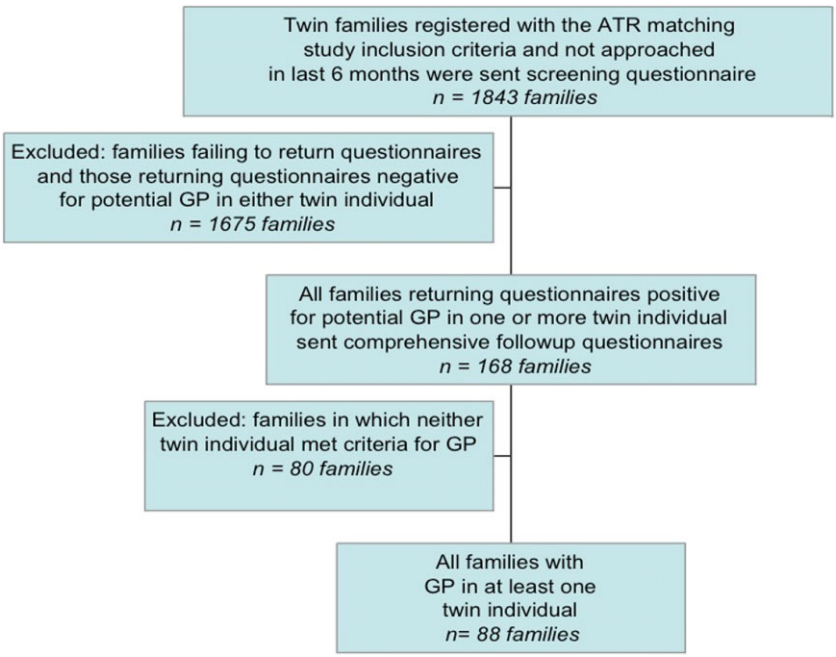

Figure 1 Subject recruitment process.

Table 1 Criteria applied for growing pains determination.

Essential growing pains criteria[a]
1. Pain in both legs
2. Pain started between the ages of 3 and 12 years
3. Pain typically occurred at the end of the day or during the night
4. There was no significant limitation of activity and no limping
Excluding factors
1. A pattern of pain severity not consistent with a diagnosis of growing pains
2. Any indication of a definite orthopaedic disorder
3. Any abnormalities on specific testing (e.g., X-rays, bone scans)
Additional descriptive features of growing pains[b]
1. Pain persisted at least 3 months
2. There were periods of days weeks or months without leg pains
3. Pain was not a problem in the morning
4. There was no associated lack of well-being

[a]If at least three of four essential growing pains characteristics were present, in the absence of any excluding factors, the individual was classified as fulfilling criteria for growing pains.
[b]Additional features for determining ambiguous cases.

particularly at night which you or your doctor think might possibly be "growing pains"?' In total, 168 families replied 'yes' and agreed to complete a more comprehensive questionnaire to assess zygosity (see below), GP and RLS.

2.2 Measures

2.2.1 Assessment of zygosity

To assess the zygosity of the twin pairs, 12 questions were asked about the general similarity between the twins (Jackson et al., 2001). The classification of zygosity was performed according to the scoring guidelines suggested by Peeters et al. (1998). The reliability of the zygosity test was assessed using internal consistency reliability estimate (Cronbach's alpha).

2.2.2 Assessment of GP

The determination of GP was based on the definition outlined by Peterson (1986) and applied in published studies, e.g., Evans (2008). In this study, four major inclusion criteria and three exclusion criteria were used to define GP (Table 1). Three additional features were included to assist in classification of ambiguous cases.

2.2.3 Assessment of RLS

Individuals with RLS were identified according to the essential criteria of the National Institutes of Health RLS diagnostic criteria for children and adults, as presented in Table 2 (Allen et al., 2003; Muhle et al., 2008). It was not practicable to incorporate the supportive criteria for RLS classification.

2.3 Data presentation and analysis

Data were analysed using IBM PASW Statistics software version 18 (IBM Corp., Armonk, NY). Means, ranges and standard deviations for selected descriptive variables were calculated (Table 3). Descriptive statistics were used to summarize the lifetime prevalence of GP and RLS in twin individuals and their participating family members (Table 4). χ^2 tests were applied to examine the association between comparison groups (e.g., zygosity and GP concordance, GP concordance and RLS status).

Table 2 Criteria for RLS in adults and children[a].

	Essential diagnostic criteria for RLS in adults		Criteria for the diagnosis of definite RLS in children
1	An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)	1	The child meets all four essential adult criteria for RLS and
2	The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting	2	The child relates a description in his or her own words that is consistent with leg discomfort (the child may use terms such as owies, tickle, spiders, boo-boos, want to run and a lot of energy in my legs to describe symptoms. Age-appropriate descriptors are encouraged.
3	The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues		
4	The urge to move or unpleasant sensations are worse during the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)		

Allen et al. (2003).
[a]Note: Supportive clinical features for definite RLS were not applied for the classification of RLS in either adults or children. RLS, restless legs syndrome.

Table 3 Characteristics of participating twin pairs.

		Age		Sex	
Zygosity	No. twin pairs (%)	Range (years)	Mean ± (SD)	Male: No. pairs (%)	Female: No. pairs (%)
MZ	34 (39)	4–14	8.4 (3.0)	17 (50)	17 (50)
DZ	54 (61)	3–16	8.4 (3.7)	12 (22) Mixed: 22 (37)	20 (37)
Total	88	3–16	8.4 (3.4)	29 (33) Mixed: 22 (25)	37 (42)

DZ, dizygotic; MZ, monozygotic, SD, standard deviation.

For assessment of the genetic hypothesis for GP, estimates of casewise concordance, the probability of being affected given co-twin affected, was calculated as

$$\text{Casewise C} = 2\text{A}/(2\text{A} + \text{B}),$$

with standard error $(\text{SE}) = \{[\text{C}(1 - \text{C})/(2 - \text{C}^2)]/(2\text{AC} + \text{B})\}^{1/2}$, where A = number of twin pairs concordant for the condition and B = number of discordant twin pairs (Witte et al., 1999).

The pedigree diagrams were generated using Pedigree-Draw: Genealogy Visualization for Macintosh software version 6 (Jurek Software, Cottage Grove, WI).

2.4 Ethics

Ethics approval was obtained from the Human Research Ethics Committee at the South Eastern Sydney and Illawarra Area Health Service.

3. Results

3.1 Sample

The second phase questionnaires were returned by 101/168 families. There were 88 twin pairs (34 MZ and 54 DZ) in which at least one twin met our diagnostic criteria of GP. The age and sex distribution of the twins are presented in Table 3.

Table 4 Twin pair concordance for growing pains (GP).

	MZ	DZ
No. pairs with GP in at least one twin	34	54
No. concordant pairs	25	12
No. discordant pairs	9	42
Pairwise concordance	0.74	0.22
Casewise concordance (SE)*	0.85 (0.06)	0.36 (0.09)

*$\chi^2 = 20.48$; $p < 0.001$.

DZ, dizygotic; MZ, monozygotic, SE, standard error.

3.2 Zygosity and characteristics of twins

Internal reliability tests revealed that questions 6 and 7 of the zygosity questionnaire were uninformative as the twins could be distinguished by all of their parents and siblings. Therefore, these two items were excluded from the analysis. The internal consistency reliability estimate (Cronbach's alpha coefficient) for the total scale was 0.93 after exclusion of these two items.

Table 3 shows that there was no difference in the average age between MZ and DZ twins.

3.3 Growing pains

Table 4 shows the concordance analysis for GP. The casewise concordance estimates differed by zygosity ($p < 0.001$), being significantly higher for MZ than DZ twins. There was no difference between male and female twin life prevalence of GP and concordance rates. Excluding twins who met criteria for both GP and RLS, the casewise concordance for GP remained significantly higher in MZ twins than in DZ twins, 0.81 and 0.35, respectively ($p < 0.01$).

For the family members of the twin pairs with GP (Table 5), there were no significant differences in the relatively high prevalence rates of GP in mothers, fathers and non-twin siblings, and these prevalence rates were not significantly different from the concordance rates of DZ twins ($p = 0.2$). Furthermore, 70% of all twin pairs with GP had at least one parent with GP.

3.4 Restless legs syndrome

More twin individuals with GP (23%) also met the criteria for RLS than twin individuals without GP (8%,

Table 5 Lifetime prevalence of GP and RLS in GP twin families.

	Mothers	Fathers	Siblings
GP	45/88 (51.5%)	32/77 (42%)	36/72 (50%)
RLS	35/87 (40%)	19/78 (24%)	13/72 (18%)

GP, growing pains; RLS, restless legs syndrome.

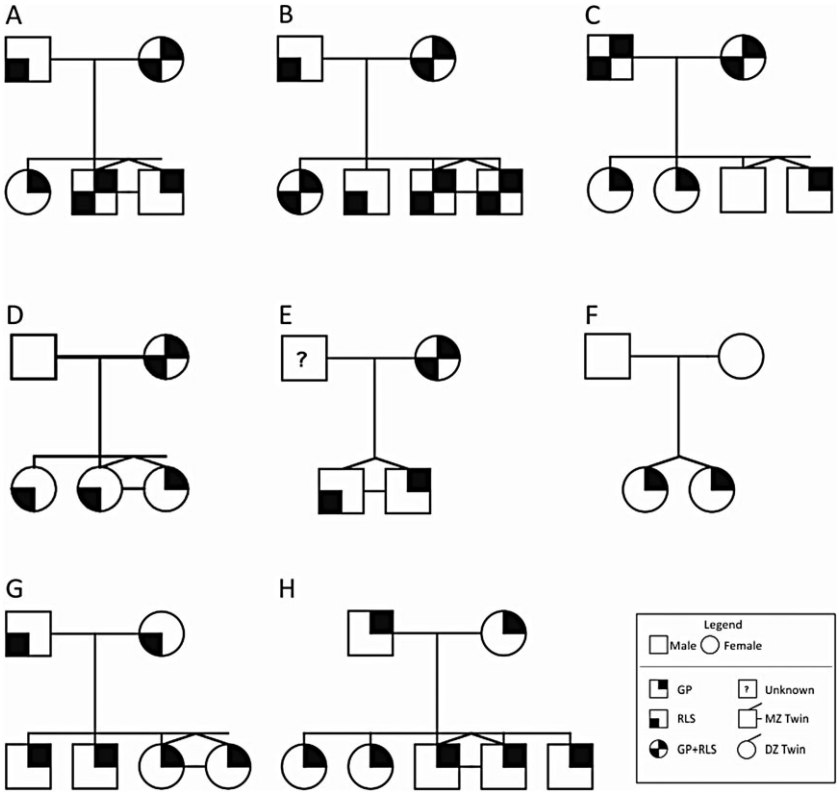

Figure 2 Illustrative pedigree diagrams of eight families.

$p = 0.03$). Seventeen of the 95 female twin individuals with GP (18%) also met criteria for RLS, which was not different from the 16 of 80 (20%) male twin individuals with GP who met criteria for RLS as well ($p = 0.9$). Significantly more GP-concordant twins also met the criteria for RLS (18%) than GP-discordant twins (2%, $p = 0.01$). Table 5 shows the number and percent of mothers, fathers and siblings with RLS in twin families with at least one twin having GP.

3.5 Pedigrees

Fig. 2 illustrates 8 of 88 pedigree diagrams selected to illustrate multi-case families of GP and within-individual and within-family relationships with RLS. Family D and E are notable for both mothers having RLS and a history of GP while one of the MZ twin pair had only GP and the co-twin had only RLS. In family F, the DZ twin daughters both had GP but neither of the parents have had RLS or history of GP, more consistent with multifactorial than with autosomal dominant genetic susceptibility.

4. Discussion and conclusions

Our primary objective was to determine whether growing pains is genetically influenced. To test this question, a twin family design was applied to children aged 3–16 years and their families. Although the peak age for GP is 4–6 years (Evans and Scutter, 2004), the condition may extend to later childhood (Uziel et al., 2010). Therefore, we were interested in lifetime prevalence of GP in twins up to 16 years, by which time, some children with GP have been shown to meet sleep study criteria for RLS (Picchietti and Stevens, 2008). The casewise concordance for lifetime history of GP of 0.85 for MZ twins compared to 0.36 for DZ twins ($p < 0.001$) supported the hypothesis of genetic susceptibility for this primary pain disorder. The prevalence of GP in relatives of twins with at least one member having GP (51.5% of mothers, 41.6% of fathers and 50% of siblings) also supported this hypothesis.

The significant difference between MZ and DZ case concordance for GP was retained after exclusion of twins who also fulfilled RLS criteria. This supported the case that GP is genetically influenced, by removing the potentially confounding of cases who, it might be argued, actually had RLS.

The secondary objective was to apply this twin family design to examine individual and familial relationships between GP and RLS. Lifetime prevalence of RLS was found in 19% of twin individuals with GP and in 40% of the mothers, 24% of fathers and 18%

of siblings of twin pairs where at least one twin had GP. Published community prevalence rates for adult RLS are 7.2–11.5% (Ghorayeb and Tison, 2010) and 2% in children and adolescents (Picchietti et al., 2007). The familial associations between RLS and GP may be due to phenotypic similarity as a consequence of shared genetic influence or to the lack of discriminatory ability of the consensus-derived, criterion-based diagnostic questionnaires.

The pedigrees showed that multi-case occurrence of GP and/or RLS was common. Only eight families had a single twin with GP and no GP or RLS in the family. We have selected eight multi-case families in Fig. 2 to illustrate close relationships between the two conditions including an example of twins with GP and parents with neither GP nor RLS, a point inconsistent with autosomal dominance of GP. The two families in which one MZ twin had GP and the other RLS underlined the close relationship between the two conditions or current inability to discriminate between them using standard questionnaires. Evidence for a relationship between childhood GP and later life RLS in individuals includes publications by Picchietti and Stevens (2008) and Balendran et al. (2011).

The results of this study have validated the pioneering observations of Brenning (1960) about relationships between GP in childhood and GP and RLS in parents. This publication could not be obtained in full until after our data were analysed. In surveys of pre-school and primary school children, features of GP had occurred in 13.6% of children aged 6–7 years and 19.8% of those aged 10–11 years, having mostly commenced by 6 years. Children with GP had one or both parents with a history of childhood GP in 51.0% compared to 12.5% for parents of children without GP. Children with GP had parents with 'molimina crurum nocturna' (a term applied to or extensively overlapping RLS) in one or both parents in 47.0% compared to 19.7% for parents of children without GP. Symptoms in the legs at night were more varied in the older children and included restlessness, tingling and cramps.

The differences between Brenning's and the present study relate mostly to methods, particularly our twin family design and the application of current questionnaires. Brenning hypothesized, as we do, that GP and RLS emanated from the central nervous system and that the connection between them was best understood 'by assuming hereditary factors as being of primary importance.'

There are limitations in this study. The criteria for GP, although widely applied in clinical practice and in research, lack extensive reliability and validity testing. Reliance on the four essential criteria for RLS, without the opportunity for individual clinical assessment, has resulted in apparent relative sensitivity of responses, without specificity determination. Furthermore, we could not account for potential parental biases in completing the questionnaires for the younger children. There is a need for improved phenotypic definition of GP in particular, and the GP and RLS questionnaires probably lack high discriminant validity. The similarities between GP and RLS are such that the diagnosis could be mistaken (Walters, 2002; Rajaram et al., 2004). The features common to both GP and RLS include pain or discomfort principally in the lower limbs at rest late in the day, no somatic pathology identified and typically normal daytime lower limb function. The major difference is the compelling urge to move the limbs and rise from bed in RLS.

Either GP or RLS are unrelated and the differentiation was inadequately specific or they are genetically related. The hypothesis that there are shared genetic determinants is supported by three particular points. There was a significantly greater association of GP-concordant twin individuals with RLS than GP-discordant twin individuals with RLS, implying greater genetic influence and association in concordant GP cases. The twin family association results for RLS were 40% for mothers, 24% for fathers and 18% for siblings (RLS typically begins in adulthood more frequently than in childhood). The pedigree diagrams, as exemplified by the selection presented, were also consistent with genetic influence on the relationship. In order to improve the evaluation of genetic aetiology of GP and of the association with RLS, we are currently conducting a twin family case–control study.

While there is a need for improved phenotypic definition of GP in particular, and the GP and RLS questionnaires probably lack sufficient discriminant validity, the data suggest that there could be shared genetic determinants between the two conditions. Perhaps a subgroup of children with GP is on the phenotypic spectrum of RLS and that the compelling urge to move the legs is not typical of younger children.

Assuming the clinical similarities and apparent genetic associations between GP and RLS, cautious inferences can be made. RLS has been considered a primary neurobiological condition (Paulus et al., 2007), perhaps generated by interacting central and peripheral abnormal inputs (Gemignani, 2010). GP might involve primary neurobiological vulnerability to pain, interacting with peripheral inputs such as from repetitive use of the legs. It is noteworthy that GP is associated with other functional pain syndromes as currently defined (Mayer and Bushnell, 2009), includ-

ing headaches and recurrent abdominal pain (Oster, 1972; Perquin et al., 2000; Rask et al., 2000; Roth-Isigkeit et al., 2004) and primary neurobiological vulnerability has been hypothesized for such multiple pain syndromes (von Baeyer and Champion, 2011).

In conclusion, this first twin study of GP has shown that the familial occurrence probably involves genetic aetiology and that this common functional pain syndrome of childhood might share genetic determinants with RLS.

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Author contributions

David Champion helped design and conduct the study, analyse the data, and write the manuscript; Shanthi Pathirana helped design the study and has been involved in the process through until the review of manuscript; Carla Flynn's and Amelia Taylor's major role was in the data entry and analysis, and also reviewed the manuscript; John L. Hopper was integral to the design of the study, approval to involve the Australian Twin Registry, advised on analysis and reviewed the manuscript; Samuel F. Berkovic was integral in the design, influential concerning genetic aspects of neurobiological disorders, contributed to methods of analysis and reviewed the manuscript; Tiina Jaaniste and Wen Qiu supervised and worked with the medical students in most aspects of the study, including data entry and analysis. Please note that all co-authors have discussed the results and commented on the manuscript.

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