Improved definition of growing pains: A common familial primary pain disorder of early childhood

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Abstract

Background: Commonly applied diagnostic criteria for growing pains (GP) have evolved without determination by an authoritative representative body. GP and restless legs syndrome (RLS) share anatomical, distributional, temporal, and other clinical features and are associated in individuals over time, in families, and in population samples. In this study, we tested the hypothesis that GP, diagnosed by widely used criteria, is confounded by cases of painful restless legs syndrome (RLS-Painful).

Methods: A twin family study of genetic influence and associations of GP using questionnaires was administered by Twins Research Australia. Twins (3–18 years; monzygous 503, dizygous 513), their oldest siblings, mothers, and fathers were randomly selected from the twin registry. Family members completed the questionnaires assessing lifetime prevalence of GP by commonly applied criteria and covariates including the history of iron deficiency and pediatric pain disorders. A GP-Specific phenotype was defined as GP without urge to move the legs. We determined similarities in twin pairs for the GP and GP-Specific phenotypes, family associations, and estimated familial and individual-specific associations for each phenotype.

Results: Lifetime prevalence was one-third lower for GP-Specific than for GP among the twin and family members. Monozygous twin pairs were more similar than dizygous twin pairs for GP and for the derived GP-Specific phenotype by three methods, consistent with genetic influence. There were familial associations, but the essential evidence for genetic influence was the twin-cotwin data. GP was associated, in multivariable analyses, with migraine, headaches, recurrent abdominal pain, and iron deficiency, while GP-Specific associations were limited to migraine and headaches.

Conclusions: GP is hybrid, one-third of cases having symptoms and associations of RLS, necessarily RLS-Painful. GP-Specific (without symptoms and associations of RLS) could have a genetic etiology. We propose new criteria to facilitate etiological and therapeutic research.

Keywords
adolescent, child, family practice, growing pains, restless legs syndrome, twin study
Key Messages

- Growing pains is a highly prevalent genetically influenced primary pain disorder of early childhood.
- Growing pains, as commonly diagnosed, is associated with restless legs syndrome in individuals over time, in families, and in population samples. The reason for this association had not previously been clarified.
- This twin family study has shown that growing pains is confounded by painful restless legs syndrome, and that an exclusion clause, urge to move the legs, results in a purer phenotype which retains genetic influence.
- On the basis of results from this study, new criteria for the diagnosis of growing pains are proposed.

1 | INTRODUCTION

Growing pains (GP), a common primary pain disorder of childhood, is characterized by periodic episodes of aching or pain felt diffusely in the limbs, mainly both lower limbs, at rest at the end of the day, and frequently interferes with sleep. Prevalence estimates have ranged widely, from 3% to 49%, depending on the methods, averaging about 15% life prevalence. There tends to be slight female preponderance, and the peak age of onset is 4–6 years. Although relatively benign, 66% experienced tearful distress at night in the case series reported by Pathirana et al. Proposed causal influences have had low-level evidence; however, GP is familial and probably genetically influenced.

Restless legs syndrome (RLS), also called Willis–Ekbom Disease, is characterized by unpleasant or uncomfortable sensations in the legs with an irresistible urge to move which achieves relief at least for the duration of the activity. Symptoms are often most severe at night when a person is resting, such as sitting or lying in bed. The current pediatric RLS criteria are presented in Box 1. Causal influences include genetic factors and iron deficiency. Prevalence estimates in children and adolescents range from 2 to 5% and are much higher in adults, particularly pregnant women.

Brenning was the first to draw attention to the relationships between GP and restless legs syndrome (RLS) and suggested genetic influences. Ekbom stated in his abstract: “There is a similarity between growing pains and the painful form of restless legs, but it is not known if these two conditions are identical.” The reported association between GP and RLS is robust, in individuals, in co-twins and family members, and in unrelated clinical samples. Children with GP attending a pediatric sleep medicine service were three times more likely to have periodic limb movements of sleep ≥5/h (an endophenotype for RLS) than controls. These data suggest that the commonly applied criteria for GP had not eliminated cases of painful RLS.

Several publications have addressed the differentiation between GP and RLS and have made clear that an important requirement is improved phenotypic definition. There is extensive overlap between the commonly applied criteria for each condition, the main point of difference being the urge to move the legs specifically in RLS (pain is not a requirement), while criteria for GP require pain in the legs. For the diagnosis of GP, a widely applied checklist of symptoms and exclusions has been applied since there has been no authoritative body formally establishing validity and consensus.

Walters, along the lines of Ekbom, posed the following question: “Is there a subpopulation of children with growing pains who really have (painful) restless legs syndrome?” It was evident that, prior to addressing any further etiological questions, potential improvement in the phenotypic definition of growing pains was required.

Our primary aim was to test the hypothesis that GP, as conventionally diagnosed by criteria, is confounded by painful RLS and that the addition of an exclusion clause of urge to move the legs (the cardinal symptom of RLS) to the diagnostic criteria for GP would result in a purer phenotype which we have termed GP-Specific. We tested the influence of this exclusion on the heritability and associations of GP. To seek further phenotypic differentiation, we performed association studies. This information will be valuable to enable improved case definition, for future etiological and therapeutic research.

2 | METHODS

2.1 | Recruitment and participants

This study is a component of a larger twin family case–control study, association analyses having been reported by Donnelly et al. Families of twins aged 3–18 years were recruited via the database of Twins Research Australia Registry (TRA). Further information about TRA can be found at: https://www.twins.org.au/research/twin-and-data-resource/70membership.

Randomly selected twin families with twins aged 3–18 years were mailed invitations to take part in the study. Accepting families were
mailed questionnaire assessments for growing pains (GP), migraine, non-migraine headache, recurrent abdominal pain, persistent pain, RLS, and history of iron deficiency. In each questionnaire pack, separate forms were provided for completion by mothers, fathers, twin individuals, and oldest non-twin siblings. A parent completed the forms for younger children and assisted older children and adolescents. The wide pediatric age range applied in this study was necessary considering the differing ages of incidence of the conditions of interest, for example, GP 2–12 years, non-iron deficiency, this was the most practical way of obtaining relevant data.

2.2 | Diagnostic criteria for growing pains (GP and GP-Specific)

To assess the current or past experience (life prevalence) of GP for each individual, a 12-item questionnaire was used, based on the diagnostic criteria described by Peterson, as applied by Evans and Scutter, Champion et al., and Donnelly et al. and as reviewed by Walters et al. Respondents were asked to rate each of the items as “true,” “false,” or “unsure.” The exclusion clause, urge to move the legs, differentiated between GP and GP-Specific. (See Box 2 and Appendix S1). The parents were instructed to discuss the urge clause, especially with younger children, and to include the response in the questionnaire to ensure that the meaning was clear in accordance with RLS criteria determination that requires the children to use their own words.

2.3 | Diagnostic criteria for other pain disorders

The diagnostic criteria applied in this study for migraine, non-migraine headaches, recurrent abdominal pain, and persistent pain are detailed in Donnelly et al. and are in Appendix S1.

2.4 | Restless legs syndrome

RLS and its subsets (phenotypes), painless and painful, is the subject of a companion paper in which the methods and criteria for the RLS categories were detailed. The only analysis about GP and RLS relationships included in this current paper concerns the association between GP and GP-Specific with mothers’ RLS (total, N = 295), painless RLS (N = 186), and painful RLS (N = 109).

2.5 | History of iron deficiency

Affirmative respondents were classified as having indicated lifetime prevalence by their parent of iron deficiency if they answered positively to both “Have you ever had iron deficiency?” and “Did a doctor diagnose it?” As we were concerned with life prevalence of iron deficiency, this was the most practical way of obtaining relevant data.

2.6 | Statistical methods

Summary statistics for DZ and MZ twins, as well as for siblings and parents, are presented by sample size and percentage, separately for cases and controls for each disorder (Table 1).
To determine whether GP or GP-Specific was influenced by genetic and/or environmental factors, we used odds ratios (OR), correlations, and casewise concordance methods to compare the similarity between MZ and DZ twins. A significantly greater similarity among MZ twins than DZ twins, under the assumption of classic twin model, shows evidence that genetic factors contribute to the variation.

Familial associations for GP or GP-Specific within twins and between a twin and his/her family member were assessed using penalized maximum likelihood logistic (PMLL) regression for combined MZ and DZ twins. A significantly greater similarity among MZ twins than DZ twins, under the assumption of classic twin model, shows evidence that genetic factors contribute to the variation.

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Correlation, concordance, and PMLL regression were conducted using the package “logistf” and TRAs own program written in R software package (http://www.R-project.org/), while all other analyses were carried out using STATA software, version 13.1 (StataCorp LP).

### RESULTS

#### 3.1 Descriptive statistics

There were 3909 randomly selected twin families who met inclusion criteria for this survey and were sent questionnaires. There were 2033 twin individuals with zygosity confirmed who had data on GP (response rate was 26%), where 1007 (49.5%) individuals were MZ twins and the remaining individuals (1026) were DZ twins. Overall, 51.6% of twin individuals were female.

In Table 1, the numbers of cases and non-cases (controls) for GP and GP-Specific are presented. Of the 687 evaluable responses from oldest siblings, 50.9% were males. There were 1013 mothers and...
922 fathers who provided data for analysis. Twins’ ages ranged from 3 to 18 years (Mean (M) = 10.5, standard deviation (SD) = 5.02); oldest siblings’ ages ranged 3–38 years (M = 12.6, SD = 17.2). Mothers’ ages ranged from 24 to 64 years (M = 42.6, SD = 6.31) and fathers’ ages ranged from 26 to 69 years (M = 44.8, SD = 6.45).

The GP lifetime prevalence in twins was within the range of published population prevalence. Overall, the application of the exclusion clause, urge to move the legs, reduced the percentage of GP cases by 34% (GP-Specific). The reduction of GP life prevalence when the exclusion clause was applied was as expected for family members and was notable for mothers (23.5%–12.7%).

When the exclusion clause was applied, urge to move the legs, reduced the percentage of GP-Specific with her/his DZ co-twin and first sibling (Table 3) probably reflect that the children shared more environmental factors with each other than with the parents.

Table 4 shows the analyses for potential genetic influence on GP and GP-Specific by three methods: common odds ratios, correlations, and by casewise concordance. The two conditions by all three tests indicated a statistically significant, higher similarity in MZ than DZ twins, consistent with genetic factors contributing to the variation.

### 3.2 Primary analyses for genetic influence

Table 2 shows the analyses for potential genetic influence on GP and GP-Specific by three methods: common odds ratios, correlations, and by casewise concordance. The two conditions by all three tests indicated a statistically significant, higher similarity in MZ than DZ twins, consistent with genetic factors contributing to the variation.

### 3.3 Familial associations and additional evidence for genetic influence

For 638 families, complete GP and GP-Specific data for oldest siblings, mother, and father were available. In Table 3, we present the results of associations (ORs) between a randomly selected twin individual and his/her co-twin, oldest sibling, mother, and father for GP and GP-Specific in all twins and separately for MZ and DZ twins.

For GP, there were statistically significant univariate associations between GP in a twin with GP in each family member group, especially the co-twin, including relatives of MZ and of DZ twins. The OR, for example, for oldest siblings of all twin individuals with GP of 4.51 shows statistically significant increase in risk of GP, a familial effect. Twin individuals, regardless of MZ or DZ status, share approximately 50% of their genes with other family members and were not expected to show MZ/DZ contrasts in family associations of GP. In the multivariable analysis, significant familial associations were found with all co-twins, MZ and DZ co-twins, but limited associations with other family members. The significant contrasts in odds ratios between MZ and DZ twins in both univariate and multivariable analyses are again consistent with genetic factors contributing to variation.

For GP-Specific, there were significant univariate associations for GP-Specific in all twin individuals, in MZ and DZ subsets, and the same condition in all family member groups, similar to that of the GP. In both univariate and multivariable analyses, the associations were most strongly for MZ subset co-twins more than for DZ subset co-twins, consistent with genetic influence.

The significant relationships (ORs) of a twin individual for GP and GP-Specific with her/his DZ co-twin and first sibling (Table 3) probably reflect that the children shared more environmental factors with each other than with the parents.

Table 4 shows the P-values for testing equality of the OR (for GP and for GP-Specific) for a twin with his/her co-twin with the OR of a twin individual with other members of the family, using the results of the multivariable model in Table 3. The MZ twin individuals had significantly higher ORs with his/her co-twin than with other family members, in contrast to the DZ twin individuals, again consistent with genetic influence. There were no significant differences between ORs for twin-sibling and for twin-mother associations, nor between ORs for twin-sibling associations and twin-father associations, and no significant differences between ORs for twin-mother and twin father associations.

### 3.4 Analysis of the combined twins and pediatric first siblings (N = 2704) associations for GP and GP-Specific with other pain disorders and with iron deficiency

Table 5 shows that, in multivariable analyses, GP was associated with three primary pain disorders, migraine, non-migraine headaches, and recurrent abdominal pain, as well as the history of iron deficiency. For GP-Specific, the only association retained was with non-migraine headache and marginally with migraine.

|                         | MZ (503 pairs) | DZ (513 pairs) | p   |
|-------------------------|---------------|----------------|-----|
| **Odds ratio**          |               |                |     |
| GP                      | OR<sub>MZ</sub> | OR<sub>DZ</sub> | .017|
| 16.4                    | (9.6,28.0)    | 6.69           |     |
| GP-Specific             | 12.0          | 9.25           | .048|
| (4.8,30.2)             | (3.3,26.2)    |                |     |
| **Correlations**        |               |                |     |
| GP                      | ρ<sub>MZ</sub> | ρ<sub>DZ</sub> |     |
| 0.53                    | (0.43,0.62)   | 0.35           | .009|
| GP-Specific             | 0.45          | 0.28           | .038|
| (0.34,0.55)            | (0.17,0.40)   |                |     |
| **Case wise concordance** |             |                |     |
| GP                      | C<sub>MZ</sub> | C<sub>DZ</sub> |     |
| 0.62                    | (0.54,0.70)   | 0.46           | .009|
| GP-Specific             | 0.53          | 0.38           | .045|
| (0.42,0.63)            | (0.27,0.48)   |                |     |

The statistically significant (p < .05) p-values are in bold.
3.5 The associations between all twins and their first siblings, GP and GP-Specific cases with their mother's history of past or present RLS, RLS-Painless, and RLS-Painful

GP in the child/offspring was significantly associated with maternal history of RLS and especially painful RLS but not with painless RLS (Table 6). GP-Specific in the child/offspring was significantly, though weakly, associated with maternal history of painful RLS, but not with RLS nor with painless RLS.

4 DISCUSSION

This study has provided evidence that GP, as previously diagnosed, is a hybrid disorder, insufficiently differentiated from RLS-Painful. This is consistent with reports of an apparent relationship between GP and RLS dating back to the publications by Brenning in 1960 and Ekbom in 1975. Prompted by publications in which concern was expressed about inadequate differentiation between the two phenotypes, and by our finding that children diagnosed with GP had a three-fold increase in periodic limb movements of sleep, we added an exclusion clause, urge to move the legs (associated with lower limb pain), the key symptom of RLS, resulting in a subset termed GP-Specific. When compared with GP, GP-Specific was shown to be a purer phenotype, retaining the indications of genetic influence while losing those associations which relate to RLS, iron deficiency, and recurrent abdominal pain. This study provides preliminary evidence that Walters was correct, there is a subpopulation of children with GP who have symptoms of RLS, necessarily RLS-Painful because lower limb pain has always been essential for the diagnosis of GP.
Approximately one-third of GP cases by commonly applied criteria had symptoms of RLS-Painful. The high lifetime prevalence estimate of GP reported by mothers (23.5%) was reduced to 12.7% (GP-Specific), reflecting the high prevalence of symptoms of RLS in pregnancy.

GP and the derivative GP-Specific were familial, as shown especially in the total samples (Table 3) and in the MZ twins, while there was also evidence for genetic influence (Tables 2, 3, and 4). Significant associations for GP and GP-Specific between DZ twin individuals and siblings (Table 3) were probably influenced by shared environment. The within-twin analyses confirmed higher, and statistically significant, similarity for MZ than for DZ twins for both GP and GP-Specific by all three methods (Table 2), with GP-Specific P-values mainly reflecting the smaller sample sizes. The familial and genetic results for GP support the findings from an earlier study, while the retained evidence for genetic influence in GP-Specific is new. The univariate associations between DZ twins and their parents suggest additionally a contribution from common environmental factors.

This study has, by definition, differentiated GP, as GP-Specific, from RLS at the individual level. It is likely that such observations as an increase in periodic limb movements of sleep in GP would no longer be found in GP-Specific. What remains to be clarified is the relationship between early childhood GP and later life RLS. We found in this study that the main contrast in maternal associations was that, in the GP-Specific phenotype, the association with

| TABLE 4 | P-values from testing of the odds ratio results in Table 3 using the multivariable model |
| --- | --- |
| Comparisons of associations (ORs) | GP | GP-Specific |
| between | ALL | MZ | DZ | ALL | MZ | DZ |
| Twin-Cotwin and Twin-Siblings ORs | <0.001 | <0.001 | 0.32 | 0.006 | 0.002 | 0.48 |
| Twin-Cotwin and Twin-Mothers ORs | <0.001 | <0.001 | 0.08 | <0.001 | <0.001 | 0.11 |
| Twin-Cotwin and Twin-Fathers ORs | <0.001 | <0.001 | 0.04 | <0.001 | 0.002 | 0.09 |
| Twin-Siblings and Twin-Mothers ORs | 0.54 | 0.88 | 0.48 | 0.31 | 0.60 | 0.39 |
| Twin-Siblings and Twin-Fathers ORs | 0.45 | 0.97 | 0.26 | 0.31 | 0.68 | 0.30 |
| Twin-Mothers and Twin-Fathers ORs | 0.85 | 0.92 | 0.62 | 0.93 | 0.93 | 0.79 |

Note: Siblings were first siblings. The Twin-Cotwin OR results support the hypothesis of genetic influence on both GP and GP-Specific. The statistically significant (p < .05) p-values are in bold.

| TABLE 5 | Multivariable analysis of the combined twins and pediatric first siblings (N = 2704) associations between GP, GP-Specific with other pain disorders and with iron deficiency |
| --- | --- |
| Predictor | GP | OR | 95% CI | P | GP-Specific | OR | 95% CI | P |
| Age | 1.04 | (1.00, 1.07) | .03 | 1.00 | (0.97, 1.03) | .97 |
| Migraine | 2.62 | (1.39, 4.94) | .003 | 1.98 | (1.00, 3.92) | .049 |
| Headache | 2.83 | (1.82, 4.38) | <.001 | 2.20 | (1.39, 3.46) | <.001 |
| Recurrent abdominal pain | 2.04 | (1.27, 3.30) | .003 | 1.62 | (0.96, 2.73) | .07 |
| Persistent pain | 0.74 | (0.38, 1.44) | .37 | 0.60 | (0.29, 1.23) | .16 |
| Iron deficiency | 2.11 | (1.08, 4.12) | .029 | 1.55 | (0.78, 3.06) | .21 |

The statistically significant (p < .05) p-values are in bold.

| TABLE 6 | Association between pediatric (twins + first siblings, N = 2706), GP (496 cases) and GP-Specific (357 cases) with mothers’ RLS total (295 cases), painless (186 cases), and painful (109 cases) |
| --- | --- |
| GP phenotypes | Mothers’ RLS condition (predictor) | OR | P | 95% CI |
| GP | RLS total | 1.57 | .001 | 1.22–2.04 |
| | RLS painless | 0.82 | .233 | 0.60–1.13 |
| GP-Specific | RLS painful | 2.92 | <.001 | 2.09–4.07 |
| | RLS total | 1.06 | .696 | 0.79–1.43 |
| | RLS painless | 0.79 | .208 | 0.55–1.14 |
| | RLS painful | 1.52 | .037 | 1.03–2.26 |

The statistically significant (p < .05) p-values are in bold.
maternal RLS (total) was lost. GP-Specific was associated only with maternal painful RLS, and this is consistent with our hypotheses that GP has been confounded by RLS-Painful and that RLS-Painful is genetically influenced.17

The authors are mindful that, notwithstanding the exclusion of the urge to move, GP-Specific has clinical similarities with RLS, especially the painful form, and there might be shared etiological mechanisms. A twin study of GP and RLS in adults and a genomics study, testing for genes associated with RLS (Jiménez-Jiménez, Alonso-Navarro, García-Martín & Agúndez24 in GP-Specific, would be appropriate. The former has been initiated. An alternative hypothesis which also merits testing is that GP is a phenotypic expression of pediatric RLS in which younger children experience dominant pain while the urge to move the legs and less pain are more likely to be experienced during adolescence.

4.1 | Strengths and limitations

The twin family design was a particular strength, enabling evidence of familial distribution including parental transmission and genetic inference. The design was also useful in testing individual and group associations, providing additional factors in phenotypic definition. There were a number of limitations to this study. The study design limits causal confirmations. The study assumed diagnoses based on questionnaires, rather than face-to-face medical interviews; this being a common issue in most epidemiological research. The response rate was relatively low, probably influenced by the number of questionnaire and the extensive family involvement. A selection bias is likely to have occurred, families with children having RLS and/or GP being more likely to respond to the survey, but this would have been unlikely to have influenced the outcomes of this study. We could not assess or control for any recall bias, but the results are clear and coherent, consistent with our hypotheses. There are inherent limitations in twin studies, but on balance, they are valuable in achieving initial evidence for genetic influence.25–27

4.2 | Implications for clinical practice

We suggest that the derived criteria for GP (see Box 2) now be applied in primary care practice and for further etiological and therapeutic research. For primary care clinicians and pediatricians with a child or adolescent presenting with nocturnal bilateral leg symptoms, the recommendation is to consider the differential diagnosis between GP as now proposed, RLS-Painful and RLS-Painless. As was shown in the companion study on pediatric RLS,17 RLS-Painful is genetically influenced, while RLS-Painless is strongly associated with female sex and iron deficiency. To what extent the more severe cases of GP and painful RLS might respond to more specific therapy for pediatric RLS28 remains to be tested.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

ETHICAL APPROVAL

Ethics approval for this study was obtained from the Human Research Ethics Committee at the South Eastern Sydney and Illawarra Area Health Service of New South Wales: HREC/14/SCHN/500—The genetic risk and associations of the primary pain disorders of childhood: a twin family case-control study.

PARTICIPANT CONSENT STATEMENT

Written informed consent was obtained from all participants. For young children who gave assent, their parents provided written consent on their behalf. Participants were advised that they may withdraw from the study at any time for any reason.

DATA AVAILABILITY STATEMENT

All authors have access to the study data. Data are available on reasonable request to the corresponding author.

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SUPPORTING INFORMATION
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