## RELATIONSHIPS BETWEEN GROWING PAINS, RESTLESS LEGS SYNDROME, MIGRAINE AND HEADACHES: A TWIN FAMILY CASE CONTROL STUDY.

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### BACKGROUND AND AIMS

Of the functional pain syndromes (FPS) of childhood, growing pains (GP) and migraine are the conditions most strongly genetically influenced. In a previous twin family study of GP conducted through the Australian Twin Registry (ATR), we obtained data supporting the conclusion that GP might share genetic determinants with restless legs syndrome (RLS). The current study involving independent twin sampling was designed to confirm this association and, applying a twin family case control design, determine whether GP is associated with other FPS, particularly migraine and headaches.

### METHOD

A cross-sectional survey of 1800 twin families (twins aged 3 – 18 years, siblings and parents) examining associations between the common FPS of childhood (particularly focusing on GP, RLS and migraine criteria) was mailed through the ATR, yielding 438 evaluable responses consisting of 235 monozygous (MZ) and 203 dizygous (DZ) twin families. Comparing families with at least one twin with GP as cases and families with neither twin having GP as controls, Chi-square tests and descriptive statistics were applied to investigate prevalence rates and associations between GP, RLS, migraine and other FPS. Concordance rates and ratios were calculated to assess heritability.

### RESULTS

There were 93 twin families with at least one twin fulfilling criteria for lifetime prevalence of GP and 345 control twin families. Of the 56 MZ twin pairs with at least one twin having GP, 26 pairs were concordant (pairwise concordance 0.46, casewise concordance 0.63). Of the 37 DZ twin pairs with at least one twin having GP, 7 pairs were concordant (pairwise concordance 0.19, casewise concordance 0.32). Although the casewise concordance was lower than we had previously reported, there was a significant difference between the MZ/DZ casewise concordance ($X^2$=6.2, $P$=0.013). Twin individuals with GP had significant associations with RLS, migraine and headache, but not recurrent abdominal pain (RAP) as tabulated.

| Twin Individuals | RLS | Migraine | Headache | RAP |
|---|---|---|---|---|
| **GP (N=126)** | 34 (27.0%) | 12 (9.5%) | 23 (18.3%) | 17 (13.5%) |
| **Controls (N=750)** | 40 (5.3%) | 35 (4.7%) | 66 (8.8%) | 79 (10.5%) |
| **Odds Ratio** | 6.6 | 2.2 | 2.3 | 1.3 |
| **$X^2$, *P*-value** | 62.8, p<0.0001 | 4.1, p=0.04 | 9.5, p=0.002 | 0.7, p = 0.4 |

In families of twin pairs with GP, 43.5% of mothers and 31.4% of fathers had a history of GP, significantly greater than in control families (*P*<0.001). RLS in mothers occurred significantly more frequently in GP families (42.4%) than in control families (*P*=0.02) while RLS in fathers did not occur more frequently in GP families (22.1%) than control families.

## CONCLUSION

The evidence that GP is genetically influenced was supported. GP was associated with RLS in twin individuals and their families, and with migraine and headache in twin individuals.

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## MIGRAINE, RESTLESS LEGS SYNDROME AND FUNCTIONAL PAIN SYNDROMES: A TWIN FAMILY CASE CONTROL STUDY.

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## BACKGROUND AND AIMS

Of the functional pain syndromes (FPS) of childhood, growing pains (GP) and migraine are the conditions most strongly genetically influenced. Restless legs syndrome (RLS) is associated with migraine, and our recent studies have shown an association also with GP. The current study, applying a twin family case control design, aimed to explore the genetic influences in migraine and to test hypotheses that migraine is associated with RLS and with other FPS of childhood.

## METHOD

A cross-sectional survey of 1800 twin families (twins aged 3 – 18 years, siblings and parents) examining associations between the common FPS of childhood (particularly focusing on GP, RLS and migraine/headache criteria) was mailed out through the Australian Twin Registry, yielding 438 evaluable responses. This study involves an analysis of the 345 control twin families (neither twin with GP) for the companion study which was a case-control study of twins with GP and their FPS associations.

Comparing families with at least one twin with migraine as cases and families with neither twin having migraine as controls, $X^2$ tests, odds ratios and descriptive statistics were applied to investigate prevalence rates and associations between

migraine, RLS and other FPS. Concordance rates and ratios were calculated to assess heritability.

## RESULTS

There were 24 twin families with at least one twin fulfilling criteria for migraine. Of the 13 monozygous (MZ) twin pairs with at least one twin having migraine, 3 were concordant (0.38 casewise concordance, 0.23 pairwise concordance). Of the 11 dizygous (DZ) twin pairs with at least one twin having migraine, 2 were concordant (0.31 casewise concordance, 0.18 pairwise concordance). The difference between MZ/DZ concordance was not significant.

There were 31 twin individuals with migraine, 5 (17.2%) who also had RLS, as opposed to 30 of the 659 (4.7%) twin individuals without migraine having RLS ($X^2$ 6.49, $P$=0.01; OR=4.2, 95% CI=1.5-11.9). Significant results were also found for the association between migraine and both recurrent abdominal pain (RAP) and chronic pain including widespread pain (CP) There were 7 (23.3%) migraine cases that reported having RAP and 63 (9.6%) migraine-free controls with RAP ($X^2$=4.5, $P$<0.001; OR=5.8, 95% CI=2.2-15.3). CP was reported in 6 (20%) cases and in 27 (4.1%) controls ($X^2$=16.9, p<0.0001; OR=6.5, 95% CI=2.6-16.5). No significant contrasts were found when comparing the prevalence of FPS in the families of twin individuals with and without migraine.

## CONCLUSION

Our results for the concordance rates of migraine in MZ and DZ twins did not add to the evidence that migraine is genetically influenced, probably influenced by the relatively small sample size . Migraine was associated with RLS, RAP and CP in twin individuals aged 3-12 years in this case-control study, consistent with current concepts of the multiple associations between FPS.

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## ASSOCIATIONS BETWEEN CHRONIC PAIN DISORDERS IN ADOLESCENTS AND HISTORY OF FUNCTIONAL PAIN SYNDROMES: A CASE-CONTROL STUDY

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## BACKGROUND AND AIMS

Functional Pain Syndromes (FPS), including growing pains (GP), recurrent abdominal pain (RAP), and non-migraine headaches, are prevalent and co-morbid in early childhood, while migraine is more frequent in adolescents than in younger

children. However, relationships between childhood FPS and chronic pain in adolescence have not been adequately examined.

This study was designed to test the hypothesis that a history of FPS will be found more often in adolescents suffering from chronic pain than in their pain-free peers.

## METHOD

Our case-control study involved 101 adolescents aged 10 to 18 years. Cases (N=46, median age 14, 65.2% female) were adolescents who were patients of the Chronic Pain Clinic with diverse chronic pain disorders. The controls consisted of 55 adolescents (median age 16, 63.6% female) who did not have chronic pain, recruited by our Schools Liaison Officer.

Case and control participants filled out questionnaires covering demographic data and known and potential risk factors for chronic pain. The diagnoses of cases were determined by self-report and chart review. To minimise inadequate or biased recall, parents were asked to report and confirm early childhood history and risk factors in their children. Questions were included to assess various FPS, as well as restless legs syndrome (RLS). A validated questionnaire screened for a history of GP.

$X^2$-tests and odds ratios were used to test the associations between chronic pain in adolescence and the lifetime prevalence of FPS. Cases in which the primary diagnosis was an extension of a FPS, *e.g.* migraine preceding chronic headache, were not included in the analysis. Multiple regression will be applied to control for other associations with chronic pain as confounders.

## RESULTS

Migraine, headache, RAP and RLS were reported significantly more frequently in cases than controls, as tabulated. The results for GP were not significant, probably reflecting the relatively small sample size.

**FPS in cases and controls**

| | **Migraine** | **Headache** | **RAP** | **GP** | **RLS** |
|---|---|---|---|---|---|
| **Cases (N=46)** | 12 (26.1%) | 14 (30.4%) | 11 (23.9%) | 9 (19.6%) | 10 (21.7%) |
| **Controls (N=55)** | 2 (3.6%) | 1 (1.8%) | 3 (5.5%) | 3 (5.5%) | 3 (5.5%) |
| **Odds Ratio** | 9.35 | 23.63 | 5.45 | 4.22 | 4.82 |
| **$X^2$, *P*-value** | .8.8, $P$=0.003 | 14.0, $P$<0.001 | 5.7, $P$=0.017 | 3.5, $P$=0.06 | 4.5, $P$=0.014 |

Other statistically significant associations with chronic pain included anxiety, depression, fatigue, adversity, injury, low iron and low vitamin D.

## CONCLUSION

When comparing controls to the sample of adolescents, the results indicate a significant association between chronic pain disorders and FPS, particularly regarding migraine, non-migraine headaches, and RAP. An association with RLS was also shown, but with this sample size GP association did not reach statistical significance.

Future research should include designs to determine the trajectory and inter-relationships between childhood FPS and testing them as independent risk factors for chronic pain in adolescents and adults.

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