*Twin Research and Human Genetics*

Article title: Shared genetic factors underlie migraine and depression

Authors: Yuanhao Yang1, Huiying Zhao1, Andrew C. Heath2, Pamela A. F. Madden2, Nicholas G. Martin3 and Dale R. Nyholt1

Authors’ information: 1Statistical and Genomic Epidemiology Laboratory, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia. 2Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA. 3Genetic Epidemiology Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia.

**Supplementary materials**

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| **Table S1 The survey questions of IHS-based migraine and DSM-based depression** |
| **IHS-based migraine** |
| Code | Abbreviation | Question |
| A | $\geq $ 5 attacks | How many (migraine/episodes of headache) have you had during your lifetime? |
| B | 4-72 hours | On average, how long (does/did) a typical (migraine/headache) episode? |
| C1 | Unilateral location | Do the headaches usually occur on one side of the head?  |
| C2 | Pulsating quality | Would you describe the headache pain you usually experience as: throbbing, pulsating or pounding? |
| C3 | Moderate/severe pain intensity | Would you describe the pain associated with your headaches as: mild, moderate, severe or unbearable? |
| C4 | Aggravation by physical activity | Are your headaches aggravated by walking up or down stairs or similar routine physical activity?  |
| D1 | Nausea and/or vomiting | Have you ever had recurrent attacks of any of the following: nausea, vomiting or diarrhoea? |
| D2 | Photophobia and phonophobia | Do you experience enhanced sensitivity to light/smell? |
| Aura\_A | $\geq $ 2 attacks with aura | How many headaches with these kinds of aura symptoms have you had during your lifetime? |
| Aura\_B | Visual/speech/sensory aura | Have you ever had: visual disturbances lasting several minutes? difficulties to speak? One sided numbness or weakness? |
| Aura\_C1 | Spreads $\geq $ 5 minutes | How fast does your visual disturbance develop: the symptom is at its worst/strongest right away (less than 1-2 minutes); or it gets worse/expands after more than 4 minutes? |
| Aura\_C2 | Last 5–60 mins | How long does your visual disturbance last: the symptom lasts less than one minute; it lasts more than one minute but less than one hour; it lasts more than one hour? |
| Aura\_C3 | Duration within 60 mins | How visual disturbances and headache connected in time are: headaches follow the symptom within one hour; headaches do not follow the symptom until later; headaches and symptom occur simultaneously; or headaches come before the symptom? |
| **DSM-based depression** |
| Code | Abbreviation | Question |
| A1 | Depressed mood | Has there ever been two weeks or more when you were depressed or down most of the day, nearly every day? |
| A2 | Loss of interest | Has there ever been two weeks or more when you were a lot less interested in most things or unable to enjoy the things you used to enjoy most of the day, nearly every day? |
| B1 | Weight/appetite change | Did you have a change in weight/appetite? |
| B2 | Sleep disturbance | Did you have more trouble sleeping than usual? |
| B3 | Psychomotor agitation/retardation | Were you so fidgety or restless that you were unable to sit still?/Were you talking or moving much more slowly than is normal for you? |
| B4 | Fatigue/loss of energy | Were you feeling a loss of energy or more tired than usual? |
| B5 | Worthlessness/feel guilty | Were you feeling excessively guilty or that you were a bad person?/Were you feeling that you were a failure or worthless? |
| B6 | Indecisiveness/diminish ability to concentrate | Were you having trouble thinking or concentrating?/Was it hard to make decisions about everyday things? |
| B7 | Suicide attempt | Were frequently thinking about death? |

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| **Table S2 Descriptive characteristics of migraine and depression**  |
|  | Total | MZFF | MZMM | DZFF | DZMM | DZFM |
| Number of twin pairs | 5319 | 1623 | 833 | 1064 | 589 | 1210 |
| mean age\* (sd) | 36.21 (11.33) | 37.99 (12.44) | 35.66 (10.59) | 36.46 (11.67) | 33.51 (8.74) | 35.27 (10.68) |

95% CI: 95% confidence interval; sd: standard deviation; MZFF: female MZ twins; MZMM: male MZ twins; DZFF: female DZ twins; DZMM: male DZ twins; DZFM: mixed-sex DZ twins. (\*) The age is calculated based on the date of sending/receiving questionnaire and/or the last update date of the questionnaire.

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| **Table S3 Summary of univariate analyses of broad migraine/depression** |
| Model | A | C (or D) | E | df | AIC | p-value |
| ***Section 1: one-threshold model*** |
| **Univariate model for broad migraine (non-migraine vs broad migraine) [5319]** |
| ACE | 0.48 (0.34–0.53) | 0\* (0–0.11) | 0.52 (0.48–0.57) | 10632 | -6919.75 | **–** |
| **AE** | **0.48 (0.43–0.52)** | **–** | **0.52 (0.48–0.57)** | **10633** | **-6921.75** | **1** |
| CE | **–** | 0.35 (0.31–0.39) | 0.65 (0.61–0.70) | 10633 | -6881.87 | 2.7×10-10 |
| ADE | 0.45 (0.21–0.52) | 0.034 (0–0.28) | 0.52 (0.47–0.57) | 10632 | -6919.83 | **–** |
| **Univariate model for broad depression (non-depressed vs broad depression) [5319]** |
| ACE | 0.40 (0.35–0.45) | 0 (0–0) | 0.60 (0.55–0.65) | 10632 | -6992.74 | **–** |
| **AE** | **0.40 (0.35–0.45)** | **–** | **0.60 (0.55–0.65)** | **10633** | **-6994.74** | **1** |
| CE | **–** | 0.28 (0.24–0.32) | 0.72 (0.68–0.76) | 10633 | -6957.64 | 1.1×10-9 |
| ADE | 0.22 (0–0.43) | 0.20 (0–0.45) | 0.58 (0.53–0.64) | 10632 | -6995.05 | **–** |
| **Univariate sex-limitation model for broad migraine (non-migraine vs broad migraine) [5319]** |
| ACE  | FM | 0.35 (0.033–0.50)0.34 (0.017–0.53) | 0.11 (0–0.39)0.093 (0–0.36) | 0.54 (0.48–0.62)0.57 (0.47–0.68) | 10629 | -7277.71 | **–** |
| **AE**  | **F****M** | **0.48 (0.41–0.54)****0.44 (0.34–0.53)** | **–****–** | **0.52 (0.46–0.59)****0.56 (0.47–0.66)** | **10631** | **-7278.18** | **0.17** |
| ADE  | FM | 0.34 (0.22–0.55)0.44 (0.14–0.53) | 0.12 (0–0.26)0.0002 (0–0.33) | 0.53 (0.46–0.61)0.56 (0.47–0.65) | 10629 | -7271.34 | **–** |
| **Univariate sex-limitation model for broad depression (non-depressed vs broad depression) [5319]** |
| ACE  | FM | 0.41 (0.31–0.47)0.094 (0–0.37) | 0.0015 (0–0.073)0.28 (0.045–0.42) | 0.59 (0.53–0.66)0.62 (0.53–0.71) | 10629 | -7060.382 | **–** |
| **AE**  | **F****M** | **0.41 (0.34–0.47)****0.41 (0.32–0.50)** | **–****–** | **0.59 (0.32–0.66)****0.59 (0.50–0.68)** | **10631** | **-7059.099** | **0.071** |
| ADE  | FM | 0.10 (0–0.37)0.41 (0.19–0.50) | 0.33 (0.046–0.47)0.0035 (0–0.22) | 0.57 (0.50–0.64)0.59 (0.50–0.68) | 10629 | -7059.996 | **–** |
| ***Section 2: two-threshold model*** |
| **Univariate model for broad migraine (non-migraine vs self-report migraine + ID migraine vs IHS MO/MA) [5319]** |
| ACE | 0.47 (0.35–0.58) | 0.080 (0–0.17) | 0.45 (0.41–0.49) | 10631 | -1229.03 | **–** |
| **AE** | **0.56 (0.52–0.60)** | **–** | **0.44 (0.40–0.48)** | **10632** | **-1228.33** | **0.10** |
| CE | **–** | 0.41 (0.38–0.44) | 0.59 (0.56–0.62) | 10632 | -1174.09 | 4.5×10-14 |
| ADE | 0.56 (0.48–0.60) | 0 (0–0.091) | 0.44 (0.40–0.47) | 10631 | -1226.33 | **–** |
| **Univariate model for broad depression (non-depressed vs MiDD vs MDD) [5319]** |
| ACE | 0.42 (0.35–0.46) | 0 (0–0.047) | 0.58 (0.54–0.63) | 10631 | -2760.71 | **–** |
| **AE** | **0.42 (0.37–0.46)** | **–** | **0.58 (0.54–0.63)** | **10632** | **-2762.71** | **1** |
| CE | **–** | 0.29 (0.25–0.33) | 0.71 (0.67–0.75) | 10632 | -2712.21 | 1.2×10-12 |
| ADE | 0.19 (0–0.41) | 0.25 (0.012–0.47) | 0.56 (0.51–0.61) | 10631 | -2764.97 | **–** |
| **Univariate sex-limitation model for broad migraine (non-migraine vs self-report migraine + ID migraine vs IHS MO/MA) [5319]** |
| ACE  | FM | 0.35 (0.19–0.63)0.044 (0–0.20) | 0.22 (0–0.35)0.36 (0.25–0.45) | 0.43 (0.35–0.48)0.59 (0.51–0.67) | 10628 | -1284.81 | **–** |
| **AE**  | **F****M** | **0.60 (0.55–0.64)****0.49 (0.40–0.55)** | **–****–** | **0.40 (0.36–0.45)****0.52 (0.45–0.60)** | **10630** | **-1285.59** | **0.20** |
| ADE  | FM | 0.60 (0.50–0.64)0.48 (0.29–0.55) | 0 (0–0.10)0 (0–0.20) | 0.40 (0.36–0.45)0.52 (0.45–0.60) | 10628 | -1281.59 | **–** |
| **Univariate sex-limitation model for broad depression (non-depressed vs MiDD vs MDD) [5319]** |
| ACE  | FM | 0.44 (0.35–0.50)0.21 (0–0.46) | 0 (0–0)0.17 (0–0.36) | 0.56 (0.50–0.62)0.62 (0.53–0.71) | 10628 | -2814.10 | **–** |
| **AE**  | **F****M** | **0.44 (0.38–0.50)****0.40 (0.32–0.48)** | **–****–** | **0.56 (0.50–0.62)****0.60 (0.52–0.68)** | **10630** | **-2816.23** | **0.39** |
| ADE  | FM | 0.12 (0–0.43)0.40 (0.14–0.48) | 0.34 (0.022–0.50)0.0026 (0–0.27) | 0.54 (0.48–0.60)0.60 (0.52–0.68) | 10628 | -2816.60 | **–** |

\*All estimates would be recorded as 0 if < 1×10-5.

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| **Table S4 Summary of univariate analyses of narrow migraine/depression** |
| Model | A | C (or D) | E | df | AIC | p-value |
| **Univariate model for IHS MO/MA (non-migraine vs IHS MO/MA) [2793]** |
| **ACE** | **0.59 (0.43–0.76)** | **0.25 (0.091–0.39)** | **0.16 (0.12–0.21)** | **5580** | **-5907.00** | **–** |
| AE | 0.86 (0.81–0.89) | – | 0.14 (0.11–0.19) | 5581 | -5899.13 | 0.0017 |
| CE | – | 0.67 (0.63–0.72) | 0.33 (0.28–0.37) | 5581 | -5863.67 | 1.7×10-11 |
| ADE | 0.86 (0.76–0.89) | 0 (0–0.093) | 0.14 (0.11–0.19) | 5580 | -5897.13 | – |
| **Univariate model for MDD (non-depressed vs MDD) [4534]** |
| ACE | 0.49 (0.43–0.54) | 0 (0–0) | 0.51 (0.46–0.57) | 9062 | -6415.92 | – |
| **AE** | **0.49 (0.43–0.54)** | **–** | **0.51 (0.46–0.57)** | **9063** | **-6417.92** | **1** |
| CE | – | 0.34 (0.30–0.38) | 0.66 (0.62–0.70) | 9063 | -6365.89 | 5.5×10-13 |
| ADE | 0.22 (0–0.48) | 0.29 (0.014–0.55) | 0.49 (0.43–0.55) | 9062 | -6420.20 | – |
| **Univariate sex-limitation model for IHS MO/MA (non-migraine vs IHS MO/MA) [2793]** |
| **ACE** | **F****M** | **0.65 (0.46–0.82)****0.43 (0.083–0.75)** | **0.19 (0.044–0.36)****0.32 (0.051–0.62)** | **0.16 (0.11–0.21)****0.25 (0.15–0.39)** | **5577** | **-6092.62** | **–** |
| AE | FM | 0.86 (0.81–0.90)0.79 (0.67–0.87) | –– | 0.14 (0.10–0.19)0.21 (0.13–0.33) | 5579 | -6089.12 | 0.023 |
| ADE | FM | 0.86 (0.71–0.90)0.79 (0.62–0.87) | 0 (0–0.15)0 (0–0.16) | 0.14 (0.10–0.19)0.21 (0.13–0.33) | 5577 | -6085.12 | – |
| **Univariate sex-limitation model for MDD (non-depressed vs MDD) [4534]** |
| ACE | FM | 0.51 (0.41–0.57)0.30 (0.012–0.55) | 0 (0–0.073)0.15 (0–0.40) | 0.49 (0.43–0.56)0.56 (0.45–0.66) | 9059 | -6498.52 | **–** |
| **AE** | **F****M** | **0.51 (0.44–0.57)****0.46 (0.36–0.56)** | **–****–** | **0.49 (0.43–0.56)****0.54 (0.44–0.64)** | **9061** | **-6501.59** | **0.63** |
| ADE | FM | 0.15 (0–0.49)0.46 (0.083–0.56) | 0.38 (0.024–0.57)0.0076 (0–0.40) | 0.47 (0.40–0.54)0.53 (0.44–0.64) | 9059 | -6501.93 | **–** |

\*All estimates would be recorded as 0 if < 1×10-5.

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| **Table S5 Summary of bivariate analyses based on best fitting model selected from univariate analyses** |
| Model | A | C (or D) | E |
| ***Section 1: one-threshold model for broad diagnoses*** |
| **Bivariate model for broad migraine and broad depression** **(non-migraine vs broad migraine & non-depressed vs broad depression) [5319]** |
| Broad migraine [AE] | 0.48 (0.44–0.53) | – | 0.52 (0.47–0.57) |
| Broad depression [AE] | 0.40 (0.35–0.45) | – | 0.60 (0.55–0.65) |
| Bivariate variance | 0.052 (0.035–0.080) | – | 2.7×10-3 (2.0×10-3–0.011) |
| correlation | 0.36 (0.27–0.45) | – | 0.067 (-4.5×10-4–0.13) |
| **Bivariate sex-limitation model for broad migraine and broad depression** **(non-migraine vs broad migraine & non-depressed vs broad depression) [5319]** |
| Broad migraine [AE] | FM | 0.49 (0.30–0.55)0.44 (0.31–0.70) | –– | 0.51 (0.34–0.70)0.56 (0.30–0.88) |
| Broad depression[AE] | FM | 0.42 (0.35–0.59)0.41 (0.30–0.51) | –– | 0.58 (0.51–0.65)0.59 (0.32–0.70) |
| Bivariate variance | FM | 0.032 (0.013–0.052)0.063 (0.013–0.13) | –– | 1.5×10-3 (1.1×10-6–0.011)3.5×10-3 (8.0×10-5–0.12) |
| Correlation | FM | 0.27 (0.16–0.79)0.39 (0.18–0.58) | –– | 0.050 (-0.063–0.29)0.077 (-0.056–0.20) |
| ***Section 2: two-threshold model for broad status*** |
| **Bivariate model for broad migraine and broad depression****(non-migraine vs self-report migraine + ID migraine vs IHS MO/MA & non-depressed vs MiDD vs MDD) [5319]** |
| Broad migraine [AE] | 0.56 (0.53–0.60) | – | 0.44 (0.40–0.47) |
| Broad depression [AE] | 0.42 (0.37–0.47) | – | 0.58 (0.53–0.63) |
| Bivariate variance | 0.055 (0.036–0.078) | – | 1.5×10-3 (3.4×10-6, 7.2×10-3) |
| correlation | 0.36 (0.29–0.43) | – | 0.050 (-0.011–0.11) |
| **Bivariate sex-limitation model for broad migraine and broad depression****(non-migraine vs self-report migraine + ID migraine vs IHS MO/MA & non-depressed vs MiDD vs MDD) [5319]** |
| Broad migraine [AE] | FM | 0.60 (0.55–0.64)0.49 (0.41–0.56) | –– | 0.40 (0.36–0.45)0.51 (0.44–0.59) |
| Broad depression [AE] | FM | 0.44 (0.38–0.50)0.40 (0.31–0.48) | –– | 0.56 (0.50–0.62)0.60 (0.52–0.69) |
| Bivariate variance | FM | 0.047 (0.026–0.074)0.058 (0.024–0.11) | –– | 4.1×10-6 (4.1×10-6–4.3×10-6)7.3×10-3 (2.1×10-5–0.028) |
| Correlation | FM | 0.33 (0.25–0.41)0.38 (0.25–0.52) | –– | 2.7×10-3 (-0.075–0.080)0.11 (5.4×10-3–0.21) |
| ***Section 3: one-threshold model for narrow diagnoses*** |
| **Bivariate model for IHS MO/MA and MDD****(non-migraine vs IHS MO/MA & non-depressed vs MDD) [N = 2406]** |
| IHS MO/MA [ACE] | 0.53 (0.35–0.72) | 0.29 (0.13–0.44) | 0.18 (0.13–0.24) |
| MDD [AE] | 0.52 (0.44–0.59) | – | 0.48 (0.41–0.56) |
| Bivariate variance | 0.13 (0.070–0.24) | – | 2.0×10-4 (8.6×10-11–0.018) |
| correlation | 0.51 (0.37–0.69) | – | -0.020 (-0.19–0.15) |
| **Bivariate sex-limitation model for IHS MO/MA and MDD****(non-migraine vs IHS MO/MA & non-depressed vs MDD) [N = 2406]** |
| IHS MO/MA [ACE] | FM | 0.60 (0.39–0.80)0.32 (0.040–0.70) | 0.23 (0.054–0.41)0.36 (0.056–0.62) | 0.16 (0.11–0.23)0.32 (0.19–0.48) |
| MDD [AE] | FM | 0.56 (0.46–0.65)0.42 (0.27–0.56) | –– | 0.44 (0.35–0.50)0.58 (0.44–0.73) |
| Bivariate variance | FM | 0.094 (0.038–0.20)0.13 (0.020–0.52) | –– | 0.016 (5.7×10-7–0.074)0.047 (1.6×10-6–0.18) |
| correlation | FM | 0.41 (0.26–0.60)0.56 (0.19–1) | –– | -0.19 (-0.41–0.036)0.29 (-8.5×10-4–0.56) |
| ***Section 4: mix-threshold model for partly narrow migraine/depression status*** |
| **Bivariate model for broad migraine and MDD** **(non-migraine vs broad migraine & non-depressed vs MDD) [N = 4534]** |
| Broad migraine [AE] | 0.48 (0.43–0.53) | – | 0.52 (0.47–0.57) |
| MDD [AE] | 0.49 (0.43–0.54) | – | 0.51 (0.46–0.57) |
| Bivariate variance | 0.073 (0.045–0.11) | – | 2.4×10-3 (8.1×10-10–8.8×10-3) |
| correlation | 0.39 (0.30–0.47) | – | 0.068 (-9.8×10-3–0.15) |
| **Bivariate model for IHS MO/MA and broad depression****(non-migraine vs IHS MO/MA & non-depressed vs broad depression) [N = 2793]** |
| IHS MO/MA [ACE] | 0.56 (0.39–0.72) | 0.28 (0.13–0.42) | 0.17 (0.12–0.22) |
| Broad depression [AE] | 0.45 (0.38–0.52) | – | 0.55 (0.48–0.62) |
| Bivariate variance | 0.097 (0.050–0.17) | – | 3.4×10-5 (4.5×10-9–0.014) |
| correlation | 0.46 (0.33–0.62) | – | -7.8×10-3 (-0.17–0.15) |

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**Figure S1**. The flow chart of selected twin sample.