*Twin Research and Human Genetics*

Article title: Shared genetic factors underlie migraine and depression

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**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 | 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 | 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 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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 | F  M | 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] | F  M | | 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] | F  M | | 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 | F  M | | 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 | F  M | | 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] | | F  M | 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] | | F  M | 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 | | F  M | 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 | | F  M | 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] | | F  M | 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] | | F  M | 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 | | F  M | 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 | | F  M | 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.