**Table S1.** Demographic and clinical characteristics of RADIANT and GSK-Munich genotyped cases.

|  |  |  |
| --- | --- | --- |
|  | **RADIANT cases**  **(N=2695)** | **GSK-Munich cases**  **(N=773)** |
| Sex (females) | 70.4 %  (N=2695) | 67.7 %  (N=773) |
| Age (y) | 44.9±12.1 (18-85)  (N=2695) | 50.7±13.7 (18-87)  (N=773) |
| Age at onset (y) | 25.2±12.0 (1-74)  (N=2695) | 35.7±13.9 (8-78)  (N=773) |
| MDD duration (y) | 19.8±13.9 (0-71)  (N=2695) | 14.9±12.1 (0-63)  (N=773) |
| Episode count | 3.8±4.8 (2-50)  (N=1966) | 4.9±4.1 (2-30)  (N=402) |
| Episode frequency (episodes/y) | 0.24±0.28 (0.03-3.0)  (N=1966) | 0.55±0.49 (0.05-3.0)  (N=402) |

Quantitative data are presented in mean±S.D. (range); y=years

**Table S2.** Familiality of (sqrt)AAO in the DeNt affected full-siblings sample:

***3-level linear mixed model (N=1403)***

*a. Model without age as covariate*

*Fixed effects*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | β | SE | p-value | 95% CI |
| Sex | 0.243 | 0.065 | <0.001 | 0.115, 0.370 |
| Intercept | 4.644 | 0.141 | <0.001 | 4.369, 4.920 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Center (n=8) | 0.146 (Vc) | 0.082 | 0.049, 0.438 |
| Family (n=683) | 0.224 (Vf) | 0.044 | 0.152, 0.329 |
| Subject error | 0.961 (Ve) | 0.050 | 0.868, 1.064 |

Familiality of sqrtAAO was documented if the variance of the random effect of family was significantly greater than zero. This was assessed with an one-tailed LRT with 1 df (Self & Liang, 1987; Stram & Lee, 1994) comparing the 3-level model with a 2-level model without the family random effect; LRT chi2(1)=29.3, p<0.001.

Family-level residual ICC= (Vc+Vf)/(Vc+Vf+Ve)= 0.278, SE= 0.054, 95% CI= 0.185, 0.395

*b. Model including age as covariate*

*Fixed effects*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | β | SE | p-value | 95% CI |
| Sex | 0.229 | 0.062 | <0.001 | 0.108, 0.350 |
| Age | 0.031 | 0.002 | <0.001 | 0.026, 0.036 |
| Intercept | 3.251 | 0.171 | <0.001 | 2.916, 3.585 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Center (n=8) | 0.122 (Vc) | 0.069 | 0.041, 0.369 |
| Family (n=683) | 0.149 (Vf) | 0.039 | 0.089, 0.248 |
| Subject error | 0.910 (Ve) | 0.047 | 0.823, 1.007 |

Familiality of sqrtAAO was similarly investigated; LRT chi2(1)=16.11, p<0.001.

Family-level residual ICC= (Vc+Vf)/(Vc+Vf+Ve)= 0.229, SE= 0.055, 95% CI= 0.140, 0.354

AAO= age at onset; Vc= center variance; Vf= family variance; Ve= error variance; LRT= Likelihood ratio test

Sex coded as 0 female 1 male

**Table S3.** Familiality of episodicity in the DeNt affected full-siblings sample:

***2-level negative binomial generalized linear mixed models (N=878)***

*a. ‘Full’ model*

*Fixed effects*

Center (n=8), Wald Chi2(7)=31.2, p<0.001 (dummy variables with deviation coding)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | coef | SE | p-value | 95% CI |
| Sex | 0.104 | 0.066 | 0.114 | -0.025, - 0.232 |
| Age | -0.023 | 0.003 | <0.001 | -0.029, -0.018 |
| Intercept | -0.426 | 0.137 | 0.002 | -0.694, -0.158 |
| Ln(MDD duration) | 1 (exposure) | | | |
| Ln(alpha)  Alpha | -1.255  0.285 | 0.093  0.026 | <0.001  <0.001 | -1.437, -1.072  0.233, 0.337 |

Sex coded as 0 female 1 male

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Family (n=486) | 0.201 (Vf) | 0.031 | 0.149, 0.271 |

We checked whether our negative binomial model fitted the observed data better than a corresponding Poisson model in two ways: first, with a LRT and, second, by testing whether the overdispersion (alpha) parameter is significantly different from zero. The LRT comparing our negative binomial model to a corresponding Poisson model was highly significant (LRT chi2(1)=591.9, p<0.001) and the overdispersion (alpha) parameter was significantly different from zero; therefore, our negative binomial model fitted the observed data better than a Poisson model.

Familiality of episodicity was documented by testing whether the variance of the family random effect was significantly greater than zero; LRT of our model vs. negative binomial regression (without the family random effect): chi2(1) = 80.47, p<0.001.

*b. ‘Reduced’ modela*

*Fixed effects*

Center (n=8), Wald Chi2(7)=39.3, p<0.001 (dummy variables with deviation coding)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | coef | SE | p-value | 95% CI |
| Intercept | -1.460 | 0.049 | <0.001 | -1.556, -1.364 |
| Ln(MDD duration) | 1 (exposure) | | | |
| Ln(alpha)  Alpha | -1.174  0.309 | 0.092  0.028 | <0.001  <0.001 | -1.354, -0.994  0.254, 0.365 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Family (n=486) | 0.227 (Vf) | 0.035 | 0.168, 0.307 |

Familiality of episodicity was similarly investigated; LRT of our model vs. negative binomial regression (without the family random effect): chi2(1) = 74.37, p<0.001.

a Model (a) without subject-level covariates, i.e. without sex and age.

Vf= family random effect variance; Vc= center variance; LRT= Likelihood ratio test

**Table S4.** Familiality of ln(episode frequency) in the DeNt affected full-siblings sample:

***3-level linear mixed model (N=878)***

*Fixed effects*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | β | SE | p-value | 95% CI |
| Sex | 0.099 | 0.060 | 0.099 | -0.018, 0.216 |
| Age | -0.026 | 0.002 | <0.001 | -0.031, -0.022 |
| Intercept | -0.398 | 0.130 | 0.002 | -0.652, -0.144 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Center (n=8) | 0.029 (Vc) | 0.019 | 0.008, 0.107 |
| Family (n=486) | 0.079 (Vf) | 0.030 | 0.038, 0.166 |
| Subject error | 0.538 (Ve) | 0.036 | 0.471, 0.614 |

Familiality of ln(episode frequency) was documented by testing whether the variance of the family random effect was significantly greater than zero. This was assessed with an one-tailed LRT with 1 df comparing our 3-level model with a 2-level model without the family random effect; LRT chi2(1)= 7.56, p=0.003.

Family-level residual ICC= (Vc+Vf)/(Vc+Vf+Ve)= 0.167, SE= 0.051, 95% CI= 0.089, 0.292

Vc= center variance; Vf= family variance; Ve= error variance; LRT= Likelihood ratio test

Sex coded as 0 female 1 male

**Table S5.** Modelling (sqrt)AAO in genotyped cases (merged RADIANT and GSK-Munich samples):

**2-level Linear Mixed Model (N=3468)**

*Fixed effects*

Study (n=5), Wald Chi2(4)=47.99, p<0.001

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | β | SE | p-value | 95% CI |
| Sex | 0.175 | 0.042 | <0.001 | 0.093, 0.257 |
| Intercept | 4.642 | 0.175 | <0.001 | 4.298, 4.986 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Center (n=21) | 0.088 (Vc) | 0.033 | 0.042, 0.186 |
| Subject error | 1.242 (Ve) | 0.030 | 1.185, 1.302 |

Testing the significance of the center random effect: LRT vs. linear regression: chi2(1) = 144.74, p<0.001

AAO= age at onset; LRT= Likelihood ratio test; Vc= center variance; Ve= error variance

Sex coded as 0 female 1 male

**Table S6.** Modelling episodicity in genotyped cases (merged RADIANT and GSK-Munich samples):

***2-level negative binomial generalized linear mixed model (N=2368)***

*Fixed effects*

Study (n=4), Wald Chi2(3)=662.55, p<0.001

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | coef | SE | p-value | 95% CI |
| Sex | 0.091 | 0.037 | 0.014 | 0.018, 0.163 |
| Age | -0.023 | 0.001 | <0.001 | -0.025, -0.020 |
| Intercept | -0.965 | 0.071 | <0.001 | -1.105, -0.825 |
| Ln(MDD duration) | 1 (exposure) | | | |
| Ln(alpha)  Alpha | -1.169  0.311 | 0.047  0.015 | <0.001  <0.001 | -1.261, -1.077  0.282, 0.339 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Center (n=12) | 0.029 (Vf) | 0.006 | 0.019, 0.044 |

Testing the significance of the center random effect: LRT vs. negative binomial regression: chi2(1) = 96.51, p<0.001

LRT= Likelihood ratio test

Sex coded as 0 female 1 male

**Table S7.** Modelling ln(episode frequency) in genotyped cases (merged RADIANT and GSK-Munich samples):

**2-level Linear Mixed Model (N=2368)**

*Fixed effects*

Study (n=4), Wald Chi2(3)=37.3, p<0.001

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | β | SE | p-value | 95% CI |
| Sex | 0.121 | 0.034 | <0.001 | 0.053, 0.188 |
| Age | -0.027 | 0.001 | <0.001 | -0.030, -0.025 |
| Intercept | -0.788 | 0.115 | <0.001 | -1.012, -0.563 |

*Random effects*

|  |  |  |  |
| --- | --- | --- | --- |
|  | variance | SE | 95% CI |
| Center (n=12) | 0.027 (Vc) | 0.015 | 0.009, 0.080 |
| Subject error | 0.561 (Ve) | 0.016 | 0.530, 0.594 |

Testing the significance of the center random effect: LRT vs. linear regression: chi2(1) = 38.72, p<0.001

LRT= Likelihood ratio test; Vc= center variance; Ve= error variance

Sex coded as 0 female 1 male

**References**

**Self SG, Liang K-Y** (1987). Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. *Journal of the American Statistical Association***82**, 605-610.

**Stram DO, Lee JW** (1994). Variance components testing in the longitudinal mixed effects model. *Biometrics* **50**, 1171-1177.