Supplementary information

A meta-analysis uncovers the first sequence variant conferring risk of Bell’s palsy

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Supplementary Figure 1. Genotypic effect of rs9357446

The odds ratio (y-axis) difference between carrier status (x-axis); non-carriers (rs9357446-GG), heterozygotes (rs9357446-AG), and homozygotes (rs9357446-AA). The whiskers represent 95% confidence interval.
Supplementary Figure 2. Manhattan plot for each dataset

Individual manhattan plots for each dataset. a) Iceland (deCODE genetics), b) the UK (UK Biobank), c) Denmark (Danish Blood Donor Study and Copenhagen Hospital Biobank), and d) Finland (Finngen). The -log₁₀P-values (y-axis) are plotted for each variant against their chromosomal position (x-axis). The red line denotes the significance level of intergenic variants, \( P \leq 7.4 \times 10^{-10} \). P values are two sided and derived from a likelihood ratio test (Methods). The variants colored green are the significant variants in the combined meta-analysis.
**Supplementary Figure 3. Locus plot for intervertebral disc disorders**

Locus plot using meta-analysis data from Iceland and the UK at the *CDC5L* locus. Variants are colored by the degree of correlation ($r^2$) with rs9357446, which is shown as a black dot. The $-\log_{10}P$-values on the left y-axis (two-sided logistic regression) are plotted for each variant against their chromosomal position (x-axis). The right y-axis shows calculated recombination rates at the chromosomal location, plotted as solid black lines.
Supplementary Table 1. Demographics for each GWAS sample in the meta-analysis.

*Mean*, *SD* standard deviation.

| Location | Gender | N (%)         | Age at first event, M (SD) |
|----------|--------|---------------|---------------------------|
| **ICE**  | Males  | 117 (40.3)    | 46.2 (24.5)               |
|          | Females| 173 (59.6)    | 47.3 (24.2)               |
| **UK**   | Males  | 983 (48.6)    | 55.4 (14.5)               |
|          | Females| 1,041 (51.4)  | 53.8 (15.4)               |
| **DNK**  | Males  | 750 (54.2)    | 52.6 (17.0)               |
|          | Females| 633 (45.8)    | 51.9 (19.9)               |
| **FIN**  | Males  | 440 (43.3)    | 52.9                      |
|          | Females| 557 (54.8)    | 50.6                      |
Supplementary Table 2. Correlated variants with rs9357446

Twenty-two variants are correlated with rs9357446 ($r^2 > 0.2$). Eleven variants are highly correlated ($r^2 > 0.9$). The $-\log_{10}P$-values show association with Bell’s palsy in the meta-analysis of Icelandic, the UK, Danish and Finnish data.

| rsName   | Position       | Effect allele | Other allele | EAF (%) | $r^2$ | D'   | -log10(P) |
|----------|----------------|---------------|--------------|---------|-------|------|-----------|
| rs9357446| chr6:44479861  | G             | A            | 44.2    | 1.00  | 1.00 | 22.2      |
| rs7770012| chr6:44479182  | C             | A            | 42.4    | 0.93  | 1.00 | 21.1      |
| rs7770034| chr6:44479267  | A             | G            | 42.2    | 0.92  | 1.00 | 21.1      |
| rs2281690| chr6:44478937  | G             | A            | 42.2    | 0.92  | 1.00 | 21.3      |
| rs6929734| chr6:44478351  | G             | T            | 41.5    | 0.88  | 0.99 | 20.6      |
| rs4714791| chr6:44473703  | T             | G            | 44.2    | 0.83  | 0.91 | 18.6      |
| rs9296437| chr6:44477359  | A             | G            | 43.1    | 0.82  | 0.92 | 18.6      |
| rs9395026| chr6:44476894  | T             | A            | 43.1    | 0.82  | 0.92 | 18.6      |
| rs9296435| chr6:44476966  | T             | C            | 43.1    | 0.82  | 0.92 | 18.6      |
| rs9296438| chr6:44477438  | A             | G            | 43.1    | 0.82  | 0.92 | 18.5      |
| rs9367197| chr6:44477709  | T             | C            | 43.1    | 0.82  | 0.92 | 18.5      |
| rs9296436| chr6:44477309  | A             | G            | 43.1    | 0.82  | 0.92 | 18.5      |
| rs9349288| chr6:44473044  | C             | T            | 46.2    | 0.75  | 0.90 | 18.0      |
| rs12154055| chr6:44481960 | G             | A            | 65.3    | 0.48  | 0.84 | 14.6      |
| rs9395021| chr6:44472985  | C             | T            | 57.0    | 0.44  | 0.86 | 12.9      |
| rs911983 | chr6:44473815  | T             | C            | 67.5    | 0.32  | 0.92 | 12.4      |
| rs10948139| chr6:44481583 | C             | T            | 60.6    | 0.30  | 0.77 | 13.5      |
| rs12664617| chr6:44484869 | C             | T            | 74.8    | 0.30  | 0.84 | 6.59      |
| rs9395025| chr6:44475625  | G             | A            | 68.0    | 0.24  | 0.80 | 11.5      |
| rs566078 | chr6:44454514  | G             | A            | 64.7    | 0.22  | 0.71 | 5.04      |
| rs543844 | chr6:44457063  | A             | G            | 65.8    | 0.20  | 0.70 | 5.33      |
| rs517214 | chr6:44456639  | A             | T            | 65.9    | 0.20  | 0.70 | 5.42      |
| rs11376630| chr6:44456591 | A             | AT           | 65.9    | 0.20  | 0.70 | 4.37      |
## Supplementary Table 3. eQTL databases

| Source                     | #/Type of tissues | #Individuals | #Genes/Type of variant | Website                                                                 |
|----------------------------|------------------|--------------|------------------------|----------------------------------------------------------------------|
| GTEx v8                    | 49               | 650          | 16.729                 | [https://gtexportal.org/home/](https://gtexportal.org/home/)           |
| Vosa et al. (2018)         | Blood            | 31,000       | 13.195                 | [https://www.biorxiv.org/content/10.1101/447367v1](https://www.biorxiv.org/content/10.1101/447367v1) |
| Strunz et al. (2018)       | Liver            | 588          | 1.299                  | [https://www.nature.com/articles/s41598-018-24219-z](https://www.nature.com/articles/s41598-018-24219-z) |
| Ratnapriya et al. (2019)   | Eye              | 453          | 5.160                  | [https://www.nature.com/articles/s41588-019-0351-9](https://www.nature.com/articles/s41588-019-0351-9) |
| Ng et al. (2017)           | Brain            | 494          | 3.041                  | [https://www.nature.com/articles/nn.4632](https://www.nature.com/articles/nn.4632) |
| Hauberg et al. (2017)      | 8                | 550          | 1.078                  | [https://www.cell.com/ajhg/fulltext/S0002-9297(17)30161-1](https://www.cell.com/ajhg/fulltext/S0002-9297(17)30161-1) |
| Zeller et al. (2010)       | Monocytes        | 1,490        | 2.745                  | [https://pubmed.ncbi.nlm.nih.gov/20502693/](https://pubmed.ncbi.nlm.nih.gov/20502693/) |
| Liang et al. (2013)        | Lymphoblastoid   | 950          | -                      | [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081280/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081280/) |
| Hao et al. (2012)          | Kidney (glomerulus) | 187      | 557                    | [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081280/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081280/) |
| Gillies et al. (2018)      | Kidney (tubulointerstitial) | 187 | 187                  | [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081280/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081280/) |
| Pala et al. (2017)         | White blood cells | 624          | 7.679                  | [https://www.nature.com/articles/ng.3840](https://www.nature.com/articles/ng.3840) |
| Yao et al. (2017)          | Whole blood      | 5,257        | 2.457                  | [https://www.sciencedirect.com/science/article/pii/S0002929717300708](https://www.sciencedirect.com/science/article/pii/S0002929717300708) |
| Franzen et al. (2016)      | Dendritic cells  | 7            | 1.823                  | [https://science.sciencemag.org/content/353/6301/827.long](https://science.sciencemag.org/content/353/6301/827.long) |
| Lee et al. (2014)          | Rested and stimulated | 534      | 171                    | [https://science.sciencemag.org/content/343/6175/1246980.long](https://science.sciencemag.org/content/343/6175/1246980.long) |
| Grundberg et al. (2016)    | 3                | 777          | 3.215                  | [https://www.nature.com/articles/ng.2394](https://www.nature.com/articles/ng.2394) |
| Ensembl Variant Effect Predictor | -                | -            | High impact            | [https://genomebiology.biomedcentral.com/articles/10.1186/s13059-016-0974-4](https://genomebiology.biomedcentral.com/articles/10.1186/s13059-016-0974-4) |
| Ensembl Variant Effect Predictor | -                | -            | Moderate impact        | [https://genomebiology.biomedcentral.com/articles/10.1186/s13059-016-0974-4](https://genomebiology.biomedcentral.com/articles/10.1186/s13059-016-0974-4) |
Supplementary Table 4. Association results from genetic correlation analysis

Significant associations between the Bell’s palsy meta-analysis and 600 published GWASs from the UK Biobank. $r_G$ genetic correlation. SE standard error.

| Trait                                    | $r_G$ | $P$        | Z-Score (SE) |
|------------------------------------------|-------|------------|--------------|
| Number of treatments or medications taken | 0.41  | $1.55 \times 10^{-8}$ | 5.66 (0.07)   |
| Overall health                           | -0.36 | $1.79 \times 10^{-7}$ | -5.22 (0.07)  |
| Body mass index                          | 0.26  | $1.52 \times 10^{-6}$ | 4.81 (0.05)   |
| Age at first sexual intercourse          | -0.28 | $2.80 \times 10^{-6}$ | -4.68 (0.06)  |
| Number of self-reported non-cancer illnesses | 0.35  | $2.95 \times 10^{-6}$ | 4.67 (0.07)   |
| Usual walking pace                       | -0.27 | $2.77 \times 10^{-5}$ | -4.19 (0.07)  |
| Endocrine diabetes                       | 0.32  | $7.23 \times 10^{-5}$ | 3.97 (0.08)   |
### Supplementary Table 5. Association results of rs9357446 with other diseases

| Phenotype                                | Cohort                              | $P$  | OR (95% CI)          |
|------------------------------------------|-------------------------------------|------|----------------------|
| Tuberculosis                             | Iceland, the UK, and Finland        | 0.012| 0.97 (0.94, 0.99)    |
| Systemic lupus erythematosus             | Iceland, the UK, and Finland        | 0.11 | 0.94 (0.87, 1.01)    |
| Multiple sclerosis                       | Iceland, the UK, and Finland        | 0.18 | 0.97 (0.92, 1.02)    |
| Asthma                                   | Iceland, the UK, and Finland        | 0.22 | 0.99 (0.98, 1.00)    |
| Ulcerative colitis                       | Iceland, the UK, and Finland        | 0.41 | 1.01 (0.99, 1.03)    |
| Type 1 diabetes                          | Iceland, the UK, and Finland        | 0.58 | 0.99 (0.94, 1.03)    |
| Chronic obstructive pulmonary disease    | Iceland, the UK, and Finland        | 0.77 | 1.00 (1.00, 1.00)    |
| Rheumatoid arthritis                     | Iceland, the UK, and Finland        | 0.81 | 0.99 (0.95, 1.04)    |
| Hypertension                             | Iceland and the UK                  | 0.87 | 1.00 (1.00, 1.00)    |
**Supplementary Note. rs9357446-A and RNA expression**

rs9357446 is located on chromosome 6p21.1. We examined *cis*-eQTL in blood and adipose tissue in Iceland (Methods) and applied Bonferroni corrected *P* value threshold based on testing 65 genes in a 5 megabase window around the variant (*P* < 0.05/65 = 7.69 × 10^{-4}). rs9357446-A significantly increases expression of Solute Carrier-Family 35 Member B2 (*SLC35B2*), located almost 222 kilobase upstream of the variant, in blood (*P* = 2.20×10^{-5}, β = 0.0540) but not in adipose tissue (*P* = 0.263, β = -0.0620). However, another variant, rs28385699-C, is the top variant affecting the expression of *SLC35B2* (*P* = 1.43 × 10^{-71}, β = -0.517), but does not significantly associate with Bell’s palsy in the meta-analysis (*P* = 1.72 × 10^{-3}, OR = 0.842). After adjusting the effect of rs9357446-A on *SLC35B2* for rs28385699-C, the *P* value is no longer significant (*P* = 7.00× 10^{-3}). Neither variant affected expression in any nearby genes in 18 other databases listed in Supplementary Table 3.
Supplementary Note. rs9357446-A and plasma proteomics

We tested associations between rs9357446-A and 4,983 plasma proteins measured in 35,559 Icelanders using SOMAscan (Methods). The strongest trans-pQTL association is with vascular endothelial growth factor (VEGF) \( (P = 1.06 \times 10^{-6}, \beta = -0.042) \) encoded by \( FLTI \). The two strongest cis-pQTL associations are with ectonucleotide pyrophosphatase/phosphodiesterase family member 5 (ENPP5) \( (P = 1.91 \times 10^{-6}, \beta = 0.040) \) and cysteine rich secretory protein 2 (CRIS2) \( (P = 3.35 \times 10^{-6}, \beta = -0.038) \) encoded by \( ENPP5 \) and \( CRISP2 \), respectively. However, rs9357446 is not the top variant affecting these proteins. VEGF is involved in vasculogenesis and angiogenesis. ENPP5 may play a role in neuronal cell communication and CRIS2 may regulate activity of ion channels.