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# The impact of genetic variations in the serotonergic system on symptom severity and clinical outcome in functional neurological disorders

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ABSTRACT

*Objective:* We studied gene-environment, as well as gene-gene interaction to elucidate their effects on symptom severity and predict clinical outcomes in functional neurological disorders (FND).
*Methods:* Eighty-five patients with mixed FND were genotyped for ten single-nucleotide polymorphisms (SNP) from seven different stress-related genes. We tested cross-sectionally the association between genotype and the symptomatology of FND (symptom severity assessed with the examiner-based clinical global impression score [CGI] and age of onset). Clinical outcome was assessed in 52 patients who participated in a follow-up clinical visit after eight months (following their individual therapies as usual). We tested longitudinally the association between genotype and clinical outcome in FND. We examined the contribution of each SNP and their interaction between them to FND symptomatology and outcome.
*Results:* We identified a nominal association between tryptophan hydroxylase 1 (*TPH1*) rs1800532 and symptom severity ($CGI_1$) in FND under a codominant model (T/T: $ß_{T/T} = 2.31$, $se_{T/T} = 0.57$; G/T: $ß_{G/T} = -0.18$, $se_{G/T} = 0.29$, $P = 0.035$), with minor allele (T) carriers presenting more severe symptoms. An association was identified between *TPH1* and clinical outcome, suggesting that major allele (G) carriers were more likely to have an improved outcome under a codominant model (G/T: $OR_{G/T} = 0.18$, $CI_{G/T} = [0.02–1.34]$; T/T: $OR_{T/T} = 2.08$, $CI_{T/T} = [0.30–14.53]$, $P = 0.041$). Our analyses suggested a significant gene-gene interaction for *TPH2* (rs4570625) and *OXTR* (rs2254298) on symptom severity, and a significant gene-gene interaction for *TPH1*, *TPH2* and *BDNF* (rs1491850) on clinical outcome.
*Conclusion:* FND might arise from a complex interplay between individual predisposing risk genes involved in the serotonergic pathway and their gene-gene interactions.

## 1. Introduction

Functional neurological disorders (FND) are among the most common neurological diagnoses [1], for which underlying mechanisms of disease aetiology still need further research. While historically trauma was advocated to play a major role in the aetiology [2], recent developments in research propose a multifactorial disease model integrating precipitating, perpetuating and predisposing factors with individual contributions from diverse psychological, neurological, and biological components for FND [3]. Despite these advancements, only little is known about potential (epi-)genetic contributions to the pathophysiology of FND. A first pilot study in FND patients identified increased oxytocin receptor (*OXTR*) methylation in FND patients [4], opening the doors for more in-depth studies in the field. Subsequent in

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situ gene-imaging studies further linked functional and structural alterations in FND patients to regional differences in transcriptional gene expression [5,6]. As such, functional network alterations in limbic-, cognitive control- and sensorimotor areas were linked to childhood physical trauma and further overlapped with the spatial distribution of expression profiles of genes involved in morphogenesis, synaptic transmission and locomotion [6]. Likewise, structural alterations in cingulo-insular and amygdala regions associated to emotional- and sexual trauma showed a high spatial correlation with adrenergic, serotonergic and oxytocinergic pathways [5]. Among the first genetic studies in FND, the allelic frequency of genetic variants in the glucocorticoid receptor gene (*NR3C1*) [7] as well as the FK506 binding protein 5 (*FKBP5*) [8] gene differed significantly in patients with functional seizures when compared to healthy controls, but not to patients with major depression. Lastly, tryptophan-hydroxylase 2 (*TPH2*) polymorphism has been associated with the symptomatology of FND potentially moderated through childhood trauma, suggesting a potential role of the serotonergic system in the disease development of FND [9]. Certain genetic polymorphisms of the serotonergic system might indeed reveal predispositions to stress-related disorders [10]. As such, genetic risk factors in combination with psychosocial risk factors such as childhood trauma might play a crucial – potentially moderating – role in the manifestation of FND in the form of a stress-diathesis model [11,12], in which individuals at risk might develop FND when certain psycho-social risk factors are present [3,11].

There is a growing interest in neuropsychiatric research in investigating certain candidate genes and their interplay with environmental factors [13] within the framework of a stress-diathesis model [14]. Such a model may help to explain why individual genetic predisposition can not only lead to the development of FND given certain environmental/psychological factors, but also represent a protective factor that contributes to understanding illness progression and recovery. Furthermore, apart from focusing on the effects of single candidate genes and their interaction with environmental factors, gene-gene interactions might add an additional level of understanding pathophysiological mechanisms [15]. Thus, we set out to first investigate a potential genetic contribution to the symptomatology and the age of onset of FND using a candidate gene approach focusing on genes associated with the stress pathways, neurotransmitters, and neuroplasticity in a cross-sectional design. Second, we aimed at investigating genetic factors associated with the clinical course of FND in a longitudinal design. Finally, we explored at gene-gene interactions in models predicting both symptomatology and long-term clinical outcomes.

## 2. Methods

The study was carried out at the University Hospital Inselspital Bern, Switzerland. A total of 86 FND patients (and 76 healthy controls) were recruited, which overlaps with previously published results on the same population [12,16–18]. Patients presented with mixed FND symptoms such as motor (ICD-10; F44.4) and sensory symptoms (F44.6), with functional seizures (F44.5), mixed symptom type (F44.7), and persistent postural-perceptual dizziness (PPPD). Exclusion criteria were: 1) major neurological comorbidities, 2) a current severe psychiatric condition (e.g., acute suicidality or psychotic symptoms), 3) alcohol or drug abuse, 4) pregnancy or breast-feeding, and 5) insufficient language skills. For the exact study design and procedure on the assessment of demographic, and clinical characteristics, we kindly refer the reader to our previous work [12,17]. On the first visit (M0), the patients underwent a clinical exam with objective assessment of symptom severity (the Simplified Version of the Functional Movement Disorder Rating Scale [S-FMDRS [19]] and the Clinical Global Impression Score [$CGI_1$] (ranging from 0 = no symptoms, to 7 = among the most extremely ill patients)) and provided a blood sample. No blood could be taken from one patient. A total of 53 Patients agreed to undergo a follow-up examination after eight months (M8) to assess their clinical outcome (description and statistical analysis for dropouts can be found in the Supplementary Material). In addition to S-FMDRS and $CGI_1$, we also performed the Clinical Global Improvement Score [$CGI_2$] (ranging from 1 = very much improved, to 4 = no change, to 7 = very much worse) at M8. All participants completed the Beck Depression Inventory (BDI [20]; at M0 and M8), the State-Trait Anxiety Inventory (STAI [21]; at M0 and M8) and the Childhood Trauma Questionnaire (CTQ [22]; at M0). For the CTQ, a total CTQ score was calculated by summing the scores of the five individual subscales. The Genotyping was conducted at the Spanish National Center for Genotyping (CeGEN, Santiago de Compostela, Spain) and is further detailed in the Supplementary Material. The study was approved by the local Ethics Committee of the Canton Bern (DRKS00012992) and conducted according to the Declaration of Helsinki. Written informed consent was provided by all subjects.

### 2.1. Clinical outcome

To delineate clinical outcomes, we classified our patients into two groups using three examiner-based measures, i.e., the S-FMDRS, $CGI_1$ and $CGI_2$ [17]. Initially, we calculated the changes in the individual scores of the S-FMDRS ($\Delta$S-FMDRS = $S\text{-}FMDRS_{M8} - S\text{-}FMDRS_{M0}$) and the $CGI_1$ ($\Delta CGI_1 = CGI_{1,M8} - CGI_{1,M0}$). Subsequently, we divided patients into two categories: those who exhibited objective clinical improvement and those who experienced either no change or a worsening in their condition, based on $\Delta$S-FMDRS, $\Delta CGI_1$ and $CGI_2$. A patient was considered as "clinically improved" if at least one of the three scores indicated an improvement, with a minimum difference of 1 point between M0 and M8. As such, 31 patients demonstrated objective clinically improvement, while 22 patients fell into the category of experiencing no change or a worsening in their clinical status, Supplementary Fig. 1. The type of therapy patients engaged in during the four weeks before M8 was assessed, Supplementary Table 4.

### 2.2. Statistical analyses

Statistical analyses were performed using *R* software (version 4.2.1.). Clinical and behavioural data were tested for normality using Shapiro-Wilk's test. Normally distributed data were analysed using two-sample *t*-test, else using Wilcoxon rank sum test. Alpha-level was set at $P < 0.05$ to determine significance. Seven genes were selected based on previous research in stress-related and mental disorders in association with childhood trauma [9,23–27]. We included two SNPs of the brain-derived neurotrophic factor (*BDNF*) gene, dopamine receptor 2/4 (*DRD2/DRD4*), two SNPs of the *FKBP5* gene, 2 SNPs of the *OXTR* gene, *TPH1* and *TPH2*, Table 1. Genotype call rate, minor allele frequency (MAF), and Hardy-Weinberg equilibrium (HWE) using chi-squared test were calculated as quality control procedure.

**Table 1**
Allele frequencies.

| Gene Symbol | SNP ID | Alleles (major/minor) | MAF [%] | *P*-HWE |
|---|---|---|---|---|
| *BDNF* | rs6265 | C/T | 17.6 | 0.715 |
| | rs1491850 | T/C | 38.2 | 0.819 |
| *DRD4* | rs3758653 | T/C | 20.0 | >0.999 |
| *DRD2* | rs1799732 | −141C Ins/Del | 10.0 | >0.999 |
| *FKBP5* | rs1360780 | C/T | 31.8 | >0.999 |
| | rs3800373 | A/C | 29.6 | >0.999 |
| *OXTR* | rs2254298 | G/A | 12.4 | >0.999 |
| | rs53576 | G/A | 42.9 | 0.657 |
| *TPH1* | rs1800532 | G/T | 46.5 | 0.514 |
| *TPH2* | rs4570625 | G/T | 21.8 | 0.751 |

$P < 0.05$ indicates statistical significance. Abbreviations: SNP: Single-nucleotide polymorphism; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium; *BDNF*: Brain-derived neurotropic factor; *DRD4*: Dopamine Receptor D4; *DRD2*: Dopamine Receptor D2; *FKBP5*: FK506 binding protein 5; *OXTR*: Oxytocin Receptor; *TPH1/2*: Tryptophan-Hydroxylase 1/2.

In a first analysis, we investigated the contribution of individual genotypes to the following clinical variables: (1) symptom severity ($CGI_1$) and (2) age of symptom onset (which represents a replication with regards to *TPH2* rs4570625 results from Spagnolo et al. [9]). For the first analysis, two separate linear regression models were conducted, each with the individual SNPs as predictor (independent) variable and either symptom severity ($CGI_1$) or age of onset as outcome (dependent) variable using *SNPassoc* [28] package in R, including age, gender, depression (BDI), trait-anxiety (STAI) and total CTQ scores as covariates. The $CGI_1$ was used as a measure for symptom severity as it accounts for all different types of symptoms (motor, sensory, seizures, vertigo), while the S-FMDRS can only account for motor symptoms. The first analysis investigating the association between genotype as predictor (independent) variable and symptom severity were thus repeated using the S-FMDRS as outcome (dependent variable) on patients with at least one motor symptom only ($N = 75$), Supplementary Table 5. For SNPs where only a few individuals were homozygous for the minor allele (i.e., less than 5), we only considered the results as relevant if they remained significant in a dominant model i.e., analysing the major allele with respect to grouping heterozygotes and homozygotes for the minor allele. In the Supplementary Material, SNPs are discussed under recessive/co-dominant models. Moreover, Supplementary Table 6 shows the genetic distribution of *TPH1* and *TPH2* compared to the healthy control population that has been collected within the framework of previous work [12,16,18]. Upon identification of significant SNPs, an additional model including an interaction term with CTQ total score was implemented. We performed subgroup analyses on patients stratified according to total CTQ score, for which a cut-off of $\geq$35 was applied according to [29]. 50 patients were classified as CTQ high ($\geq$ 35), and 35 patients presented with CTQ low ($<$ 35).

Second, we examined a potential association between genotype and clinical outcome. Thus, we performed a logistic regression using *SNPassoc* [28] package with the individual SNPs as predictor (independent) variable and clinical outcome (dichotomized; improved vs. no change/worsened) as outcome (dependent) variable, including age, gender, depression, trait-anxiety and total CTQ score as covariates.

In a third analysis, the combined effect and interaction between SNPs and binary independent variables (i.e., clinical outcome) were also tested using the multifactorial dimensionality reduction system (MDR; https://sourceforge.net/projects/mdr/files/mdrdt/), to define the best interaction models for our analyses. MDR reduces high-dimensional multi-locus genetic data into a single dimension. MDR is optimized to detect gene-gene or gene-environment interactions in (binary) case-control studies [30]. Thus, MDR can be used to identify interactions even in the absence of a main effect of selected genes. A 2-to-3 interaction model was considered, and a 10-fold cross validation (CV) procedure was applied to ensure a robust evaluation of the model's predictive performance. In this approach, the dataset is divided into ten subsets, and the model is trained and tested iteratively on different combinations of these subsets. CV is preferred when data is limited as it effectively simulates the use of an independent test set. Therefore, this method mitigates overfitting and provides a more reliable estimate of how the model generalizes to unseen data. The performance of the model was assessed using *balanced accuracy*, which is the average of the model's accuracy across all cross-validation folds [30].

The identified interaction model was then tested using multiple logistic/linear regression models with a stepwise selection procedure adding the covariates (which is not possible within MDR). This procedure systematically added and removed predictors based on their statistical significance to identify the model that best explains the interaction between SNPs and 1) symptom severity, 2) age of onset, and 3) clinical outcome, including age, gender, depression, trait-anxiety and total CTQ score as covariates. An explanatory code can be found on https://github.com/webersamantha/GeneticVariations_FND.

## 3. Results

### 3.1. Clinical, demographic, and genetic characteristics

This study included genomic data (derived from EDTA whole blood samples) from 85 FND patients (no blood was taken from one patient at baseline). Demographic and clinical characteristics are presented in Table 2. Fifty-two Patients returned for a follow-up visit where questionnaires and the clinical examinations were repeated, Table 3. Compared to patients who did not complete the study (i.e., the follow-up), the included patients showed lower state-anxiety scores (Supplementary Table 2, Supplementary Fig. 1) but were comparable regarding all other demographic variables. During the time between M0 and M8, patients engaged in one or more kind of therapy at which psychotherapy (57 %) and physiotherapy (43 %) was most common (Supplementary Table 4). Genotype success rate was 100 % for all subjects, and SNPs were in HWE ($P < 0.05$), Table 1.

**Table 2**
Demographic and clinical data.

| | FND ($N = 85$) |
|---|---|
| Age, mean (SD), years, [range] | 37.53 (14.24), [17–77] |
| Sex (females/males) | 63/22 |
| Disease severity ($CGI_1$, median, quantile) | 2 [1–4] |
| Duration of illness (in months)[a] | 58.78 (72.99) |
| Symptom type[b] | 44 sensorimotor<br>24 gait disorder<br>17 tremor<br>12 myoclonus<br>14 PNES<br>8 dystonia<br>7 PPPD<br>5 speech disorder<br>2 functional deafness<br>1 functional vision loss |
| ICD-10 Classification[c] | 62 F44.4<br>7 F44.5<br>29 F44.6<br>8 F44.7<br>6 PPPD |
| Psychotropic medication | 14 benzodiazepines<br>29 antidepressants<br>6 neuroleptics<br>9 antiepileptics<br>6 opioids |
| BDI score, mean (SD) | 14.36 (9.99) |
| STAI-S score, mean (SD) | 37.06 (10.93) |
| STAI-T score, mean (SD) | 45.31 (13.00) |
| CTQ total score, mean (SD) | 43.01 (17.02) |
| Emotional Abuse, mean (SD) | 10.12 (5.17) |
| Emotional Neglect, mean (SD) | 11.14 (5.15) |
| Physical Abuse, mean (SD) | 7.15 (3.88) |
| Physical Neglect, mean (SD) | 7.68 (3.06) |
| Sexual Abuse, mean (SD) | 6.92 (3.89) |

Abbreviations: BDI = Beck's depression inventory; $CGI_1$ = Clinical Global Impression Score; $CGI_2$ = Clinical Global Improvement Score; CTQ = Childhood trauma questionnaire; ICD-10 = Internation Classification of Diseases Version 10; M0 = Baseline; M8 = Follow-up after eight months; SD = Standard deviation; S-FMDRS = Simplified Version of the Functional Movement Disorder Rating Scale; STAI-S/−T = State-Trait Anxiety Inventory; PNES = Psychogenic non-epileptic seizures; PPPD = persistent postural-perceptual dizziness.

[a] This includes the time from the appearance of the first symptoms until study date. Patients reported on several years between appearance of the first symptoms until being properly diagnosed. This long duration might represent rather a failure of timely getting diagnosed than a chronicity of the patients' disorder.

[b] Patients can present with several symptom types.

[c] Diagnosis of mixed FND (F44.7) was given when F44.4, F44.5, and F44.6 was present.

**Table 3**
Demographic and clinical data of patients participating in follow-up.

| | M0 (N = 52) | M8 (*N* = 52) | Statistics |
|---|---|---|---|
| Age, mean (SD), years, [range] | 37.78 (14.58) [19–77] | – | – |
| Sex (females/males) | 37/15 | – | – |
| Disease severity ($CGI_I$, median, quantile) | 2 [1–4] | 2 [1–4] | $P = 0.528$ |
| Disease improvement ($CGI_{II}$, median, quantile) | – | 4 [3–4] | – |
| Disease severity (S-FMDRS, median, quantile) | 6 [0–12.25] | 6 [0–11] | $P = 0.966$ |
| Duration of illness (in months, SD) | 57.04 (61.10) | – | – |
| Symptom type[a] | 25 sensorimotor<br>16 gait disorder<br>8 seizures<br>7 tremor<br>7 myoclonus<br>4 PNES<br>6 PPPD<br>5 speech disorder<br>4 dystonia<br>1 functional vision loss | | |
| ICD-10 Classification[b] | 36 F44.4<br>4 F44.5<br>19 F44.6<br>5 F44.7 | | |
| Psychotropic medication | 8 benzodiazepines<br>19 antidepressants<br>3 neuroleptics<br>5 antiepileptics<br>4 opioids | | |
| BDI score, mean (SD) | 12.98 (9.78) | 12.19 (10.84) | $P = 0.367$ |
| STAI-S score, mean (SD) | 35.02 (10.55) | 36.13 (11.06) | $P = 0.630$ |
| STAI-T score, mean (SD) | 43.57 (13.21) | 42.13 (13.42) | $P = 0.211$ |

Abbreviations: BDI = Beck's depression inventory; $CGI_1$ = Clinical Global Impression Score; $CGI_2$ = Clinical Global Improvement Score; ICD-10 = Internation Classification of Diseases Version 10; M0 = Baseline; M8 = Follow-up after eight months; SD = Standard deviation; S-FMDRS = Simplified Version of the Functional Movement Disorder Rating Scale; STAI-S/−T = State-Trait Anxiety Inventory; PNES = Psychogenic non-epileptic seizures; PPPD = persistent postural-perceptual dizziness.

[a] Patients can present with several symptom types.

[b] Diagnosis of mixed FND (F44.7) was given when F44.4, F44.5, and F44.6 was present.

### 3.2. Genetic association with symptom severity

A nominal association ($P < 0.05$) was identified between symptom severity and 1) rs4570625 in the *TPH2* gene (codominant model: $\beta_{T/T} = 2.31$, $se_{T/T} = 0.57$, $\beta_{G/T} = -0.18$, $se_{G/T} = 0.29$, $P = 0.035$) with TT-carriers (minor allele) having more severe symptoms and GT-carriers having less severe symptoms compared to GG-carriers. No interaction with CTQ total score was found. However, for this model, it must be considered that only $N = 3$ subjects were homozygote for the minor allele (TT), which were strongly driving the results. Upon removal of these subjects or grouping of TT-carriers with GT-carriers, the results did not remain significant. Further, a significant association was found between symptom severity and 2) rs1800532 in the *TPH1* gene (recessive model: ß = 0.85, se = 0.34, $P = 0.034$), with a higher symptom severity in TT-carriers (minor allele) compared to GT and GG-carriers, Table 4.

Significance code: $***P < 0.001$, $**P < 0.01$, $* P < 0.05$, $\bullet P < 0.1$

Additionally, a significant interaction with the minor allele of *TPH1* rs1800532 and childhood trauma was observed in the association with symptom severity ($P = 0.004$). Upon stratification according to total CTQ score, a significant association with symptom severity (CGI) was found in patients with low CTQ total scores while no association was found in subjects with high CTQ scores. Indeed, TT carriers were found to have higher symptom severity compared to GG or GT but only in the CTQ – low group (Table 5, Fig. 1).

### 3.3. Genetic association with clinical outcome and age of onset

Using a logistic regression analysis, we identified a significant association between the dichotomized clinical outcome variable and rs1800532 in the *TPH1* gene (codominant model: $OR_{G/T} = 0.18$, $CI_{G/T} = [0.02–1.34]$, $OR_{T/T} = 2.08$, $CI_{T/T} = [0.30–14.53]$, $P = 0.041$) with TT-carriers (minor allele) being more likely to have a worse/unchanged outcome after eight months, Table 4. No interaction with CTQ total score was found. No significant associations were found between any of the SNPs and age of onset in FND patients.

### 3.4. The influence of SNP interactions on symptomatology

To investigate on the best interaction model for SNPs and symptomatology (i.e., symptom severity [$CGI_1$] and clinical outcome in FND), a stepwise linear regression was performed. First, using symptom severity ($CGI_1$) as outcome measure, two SNPs remained significantly associated using a codominant model rs4570625 (*TPH2*) and rs2254298 (*OXTR*) with *TPH2* TT-carriers and *OXTR* GA-carriers conjointly contributing to higher symptom severity. Second, using age of onset as outcome measure in the multiple linear regression, none of the SNPs remained significant. Third, none of the SNPs remained significantly associated when using clinical outcome as independent variable within the multiple logistic regression.

When using MDR, investigating SNP-SNP interactions on clinical outcome, the best model appeared to be a three-locus interaction model including rs1491850 (*BDNF*), rs1800532 (*TPH1*) and rs4570625 (*TPH2*) with a maximum CV consistency of 9/10 and the highest testing balanced accuracy of 70 %. Fig. 2 illustrates the three-SNP model and indicates the best genotypic combinations regarding clinical outcome. As MDR is a machine learning based approach, we retested those SNPs which appeared optimal within MDR using a multiple logistic regression model, with and without including covariates. None of the SNPs remained significant, which might indicate a highly non-linear and complex pattern of interaction, which cannot be captured by linear models.

## 4. Discussion

The serotonergic pathway has been subject to scientific studies, in which polymorphisms have been associated with increased risk of developing neuropsychiatric disorders [31]. As serotonin has a well-known relevance in the stress response, it is believed that genes involved in the serotonin system may unveil a condition of susceptibility to stress-related disorders along with the potential effect of stress-inducing life events like childhood trauma [10].

Mechanistically, the metabolism of serotonin is strictly regulated by two pathways: the serotonergic pathway (resulting in the production of serotonin) and the kynurenine pathway, which metabolizes about 95 % of free tryptophan [32], see Fig. 3 for serotonergic pathway. On a molecular level, chronic stress (i.e., corticosteroids/cytokines) was found to activate enzymes in favour of catalysing the kynurenine pathway (e.g., IDO1/2) over the serotonin pathway, which further leads to the depletion of serotonin [33]. As such, serotonin synthesis might be reduced under basal or stressful conditions, and the ability to counteract the detrimental neurobiological effects of stress will be consequently diminished [34]. This effect might be enhanced in subjects with the risk alleles of *TPH1/TPH2* genetic variants. In particular, alterations in the stress response [35] as well as in the HPA-axis [12] have been identified in FND.

**Table 4**
Association analysis between SNP and FND symptom severity and clinical outcome.

| Outcome variable | SNP ID | Gene | Model | Genotype | Full FND sample cross-sectional ($N = 85$) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Cases | β (se) | *P*-value |
| Symptom Severity ($CGI_I$) | rs4570625 | *TPH2* | Recessive | G/G-G/T | 82 | 0.00 | 0.011* |
| | | | | T/T | 3 | 2.36 (0.57) | |
| | | | Codominant | G/G | 51 | 0.00 | 0.035* |
| | | | | G/T | 31 | −0.18 (0.29) | |
| | | | | T/T | 3 | 2.31 (0.57) | |
| | rs1800532 | *TPH1* | Recessive | G/G-G/T | 65 | 0.00 | 0.033 * |
| | | | | T/T | 20 | 0.85 (0.34) | |

| Outcome variable | SNP ID | Gene | Model | Genotype | Full FND sample longitudinal ($N = 52$) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Cases | | OR [95 % CI] | *P*-value |
| | | | | | $G_{Imp}$ | $G_{Wor}$ | | |
| Clinical outcome | rs1800532 | *TPH1* | Codominant | G/G | 9 | 8 | 1.00 | 0.041 * |
| | | | | G/T | 16 | 7 | 0.18 [0.02–1.34] | |
| | | | | T/T | 5 | 7 | 2.08 [0.30–14.53] | |

Abbreviations: $CGI_1$ = Clinical Global Impression Score; $G_{Imp}$ = Improved; $G_{Wor}$ = Worse or remained stable; OR = Odds ratio; SNP = Single nucleotide polymorphism; *TPH1/2* = Tryptophan-Hydroxylase 1/2.

**Table 5**
Association analysis between SNP and high CTQ scores.

| Outcome variable | SNP ID | Model | Genotype | CTQ High sample ($N = 50$) | | |
|---|---|---|---|---|---|---|
| | | | | Cases | β (se) | *P*-value |
| Symptom Severity ($CGI_1$) | rs1800532 | Recessive | G/G-G/T | 37 | 0.00 | 0.770 |
| | | | T/T | 13 | 0.14 (0.35) | |
| | | Codominant | G/G | 17 | 0.00 | 0.464 |
| | | | G/T | 20 | −0.59 (0.37) | |
| | | | T/T | 13 | −0.17 (0.35) | |

| | | | | CTQ Low sample ($N = 35$) | | |
|---|---|---|---|---|---|---|
| | | | | Cases | β (se) | *P*-value |
| Symptom Severity ($CGI_1$) | rs1800532 | Recessive | G/G-G/T | 28 | 0.00 | 0.004** |
| | | | T/T | 7 | 1.92 (0.57) | |
| | | Codominant | G/G | 9 | 0.00 | 0.018* |
| | | | G/T | 19 | 0.26 (0.36) | |
| | | | T/T | 7 | 2.12 (0.57) | |

Abbreviations: $CGI_1$ = Clinical Global Impression Score; CTQ = Childhood trauma questionnaire; SNP = Single nucleotide polymorphism.
Significance code: ***$P < 0.001$, **$P < 0.01$, * $P < 0.05$, • $P < 0.1$.

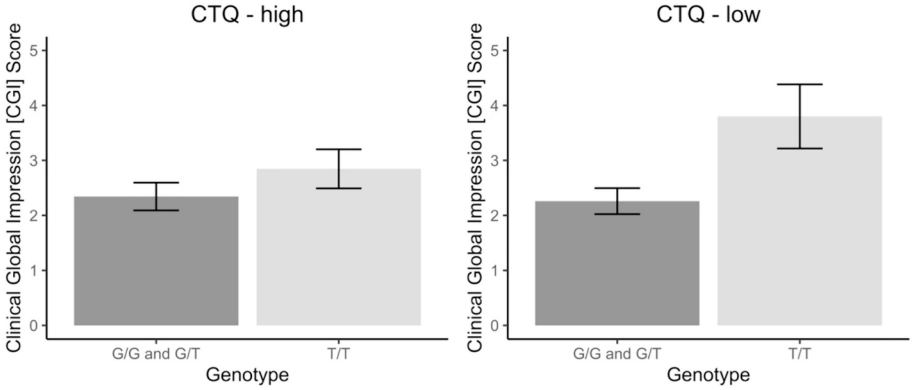


**Fig. 1.** Effect of *TPH1* genotype and childhood trauma on symptom severity (Clinical Global Impression [$CGI_1$] Score). A total of 50 patients were classified as CTQ high (> 35, left), and 35 patients presented with CTQ low (≤35, right). Bar plots show mean and standard error of $CGI_1$.

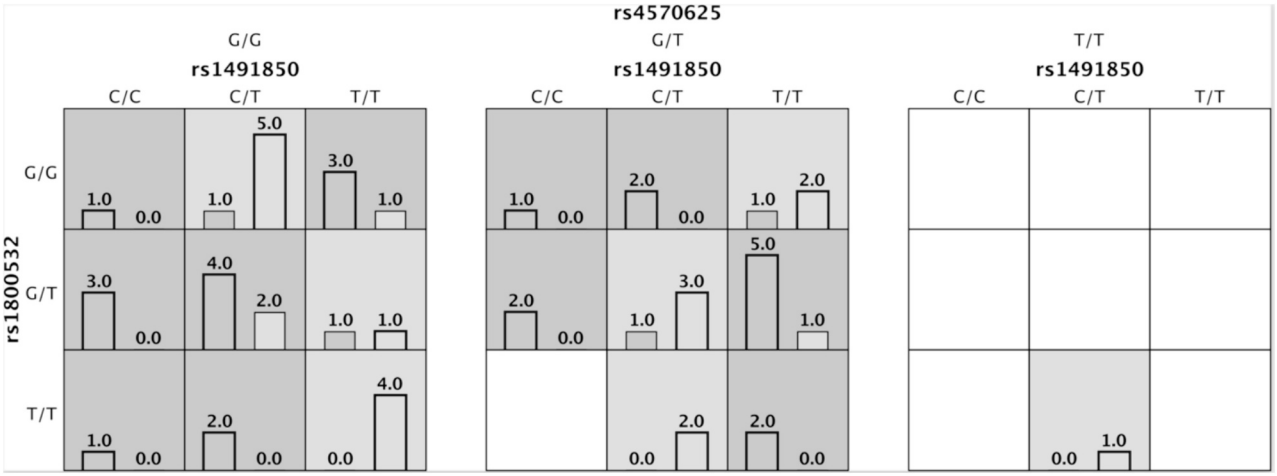


**Fig. 2.** Summary of three-locus genotype combination associated with clinical outcome in FND. Bars in cells represent distributions of improved (left) and worse/unchanged (right) clinical outcomes with each multifactor combination. Dark-shaded cells represent genotype combinations with increased likelihood of improved outcome, whereas light-shaded cells represent genotype combinations with decreased likelihood of improved outcome. White cells represent genotype combinations for which no data were observed. The following genotype combinations were associated with a worse/unchanged clinical outcome (light shading): 1) rs1491850 CT (*BDNF*), rs1800532 GG (*TPH1*) and rs4570625 GG (*TPH2*); 2) rs1491850 TT (*BDNF*), rs1800532 GT (*TPH1*) and rs4570625 GG (*TPH2*); 3) rs1491850 TT (*BDNF*), rs1800532 TT (*TPH1*) and rs4570625 GG (*TPH2*); 4) rs1491850 TT (*BDNF*), rs1800532 GG (*TPH1*) and rs4570625 GT (*TPH2*); 5) rs1491850 CT (*BDNF*), rs1800532 GT (*TPH1*) and rs4570625 GT (*TPH2*); 6) rs1491850 CT (*BDNF*), rs1800532 TT (*TPH1*) and rs4570625 GT (*TPH2*); and 7) rs1491850 CT (*BDNF*), rs1800532 TT (*TPH1*) and rs4570625 TT (*TPH2*). Abbreviations: BDNF = Brain-derived neurotrophic factor; TPH1/2 = Tryptophan-Hydroxylase 1/2.

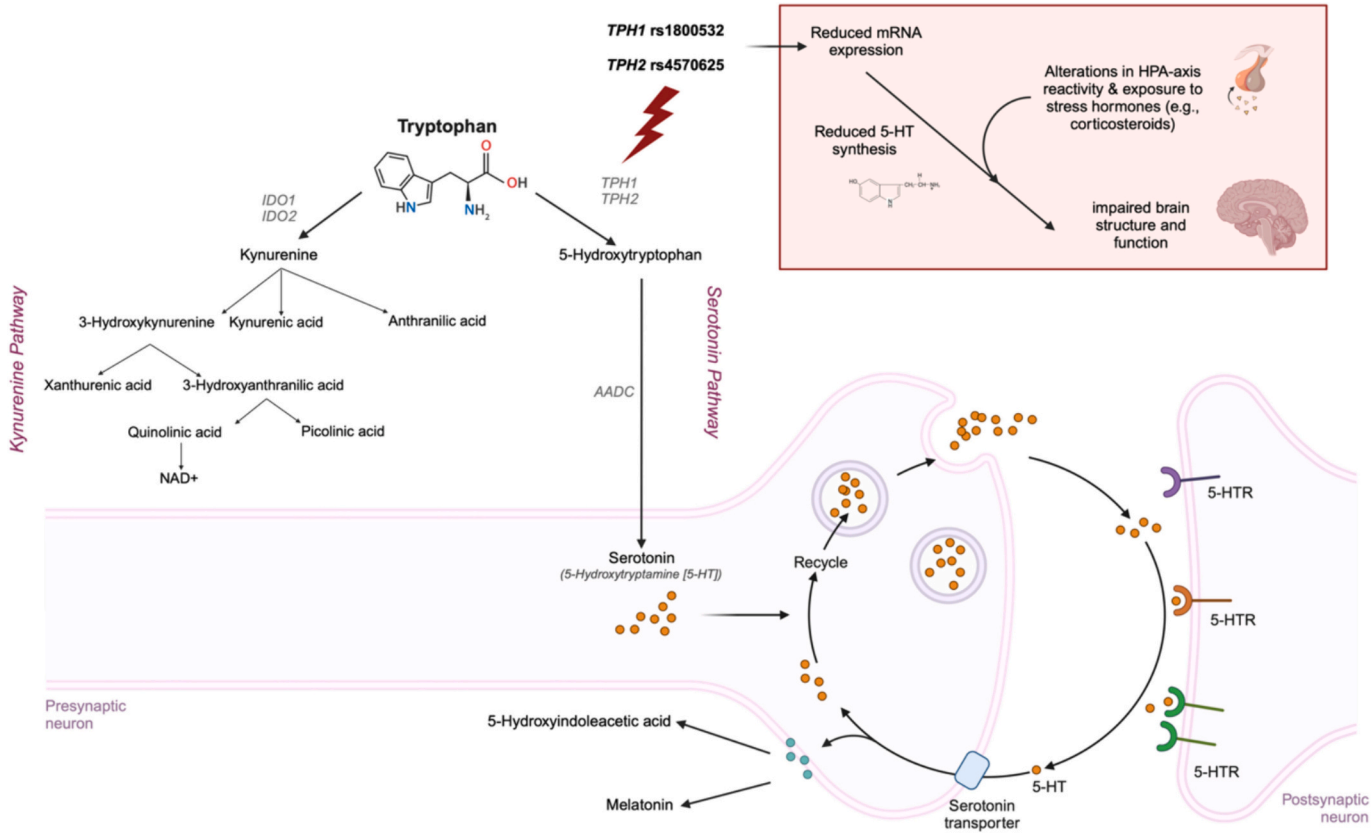


**Fig. 3.** The serotonergic pathway. The essential amino acid tryptophan might be metabolized either through the kynurenine pathway (95 %) or through the serotonergic pathway [32]. In the serotonergic pathway, tryptophan is converted into 5-hydroxytryptophan (5-HTP) catabolized by the tryptophan hydroxylase 1/2 (TPH1, TPH2). The *TPH1* and *TPH2* genes code for rate-limiting enzymes in the biosynthesis of serotonin, at which the *TPH1* rs1800532 T-allele is suggested to alter mRNA transcription in a way that could reduce serotonin levels [36]. Aromatic acid decarboxylase (AADC) then further decarboxylases 5-HTP to 5-hydroxytryptamine, i.e., serotonin (5-HT). Upon release into the synaptic cleft, serotonin can bind to the serotonin receptors (5-HTR) on the postsynaptic membrane, or is re-uptaken through the serotonin transporter, where it is either recycled or further metabolized [32]. Alternatively, tryptophan might be converted into kynurenine by the indoleamine 2–3-dioxygenase 1/2 (IDO1, IDO2) and further converted in its diverse downstream metabolites, such as kynurenic acid, which exhibits neuroprotective effects [37]; or quinolinic acid, which exhibits neurotoxic effects [38]. Illustration has been created with BioRender (https://biorender.com/).

### 4.1. Interaction between TPH2 (rs4570625) and OXTR (rs2254298)

The previous study by Spagnolo et al. [9] showed that the rs4570625 T-allele of the *TPH2* gene had a main effect on functional movement disorder (FMD) manifestation and might modulate it through the interaction with childhood trauma. Particularly, rs4570625 T-allele carriers had a significantly lower age of onset compared to patients homozygous for the G-allele. As this result was only partially replicated in three subjects of our cohort with respect to symptom severity, we speculate that this might be due to the fact that our patients displayed a more heterogeneous clinical phenotype than in the previous work [9], in which exclusively FMD patients were included. When focusing on motor symptoms only and using the S-FMDRS as a measure for symptom severity (which accounts more directly for motor symptoms than $CGI_1$), the results appeared consistent within subgroups of FND patients and, correspondingly, with different measurements of symptom types. As regards to symptom severity in the previous work, *TPH2* rs4570625 did not show a significant association by itself in FMD patients, however, higher self-reported childhood traumata were associated with increased severity of FMD symptoms in T-allele carriers. Similarly, we identified a significant interaction between T-allele carriers of the *TPH1* rs1800532 and the CTQ total score. As by example, among subjects carrying rs1800532 T-allele, increasing severity of abuse was associated with the severity of psychopathology [34]. Thus, it has been hypothesized that this genetic variation might have an influence on serotonergic dysfunction, leading to a differential response to environmental stressors.

Furthermore, our analysis revealed a significant two-fold interaction model with *TPH2* rs4570625 TT and *OXTR* rs2254298 GA combined genotypes presenting a higher FND symptom severity. In view of previous studies, *OXTR* variants have been reported to be associated with stress predisposition [39]. Thus, it was suggested that the effects of *OXTR* might be largely mediated by its influence on psychological resources known to buffer the detrimental effects of stress that could conduct to the development of neuropsychological and neuropsychiatric disorders [40]. Several reports have associated the *OXTR* rs2254298 polymorphism, and its interaction with early environmental context with differential risk for neuropsychiatric disorders [39]. It has been suggested that *OXTR* rs2254298 A-allele carriers might be more susceptible to the effects of adverse environmental exposures than the GG homozygotes for this SNP, resulting in a higher risk of suffering from emotional psychopathologies [41]. As part of the discussion on the implications of *OXTR* rs2254298 on the risk of developing psychopathologies, it has been proposed that the minor allele of this variant might confer a differential susceptibility to early environmental conditions rather than increased vulnerability for neuropsychiatric disorders, meaning that depending on the environmental context the same allele could predispose to a higher psychopathological risk or a more favourable functional outcome [39]. Overall, the combined effect of *TPH2* and *OXTR* polymorphisms together with prolonged stress exposure and reduced psychological resources might add evidence supporting our findings regarding the association of rs4570625 and rs2254298 with symptom severity in FND patients.

### 4.2. Interaction between TPH1 (rs1800532), TPH2 (rs4570625) and BDNF (rs1491850) involved in clinical outcome in FND

Apart from a significant association of symptom severity as well as clinical outcome with *TPH1* rs1800532, further insights emerged from our analysis using MDR for model selection, which suggested a potential interaction between *TPH1* rs1800532, *TPH2* rs4570625 and *BDNF* rs1491850 with an accuracy of 70 %. The *BDNF* rs1491850 SNP lays within a gene encoding the brain-derived neurotrophic factor (*BDNF*) that was found to be implicated in neuronal survival, differentiation, axonal and dendritic growth, plasticity and apoptosis, in neurons of the central nervous system in general, and of the serotonergic system in particular [42]. These findings propose a biological path in which *BDNF* and *TPH* genes may interact.

Only few studies in neuropsychiatric disorders focused on genetic effects on clinical outcome. As such, *BDNF* rs1491850 T-allele was more prevalent among treatment-resistant patients with major depressive disorder (MDD) [43], as well as in patients with obsessive-compulsive disorders [44]. Furthermore, in patients with social anxiety disorder, it was demonstrated that the *TPH2* rs4570625 GG homozygotes were linked to significantly greater improvement in anxiety symptoms when treated with placebo, in comparison to T-allele carriers [45]. The underlying explanation for this could be that specific genotype combinations of *TPH2* rs4570625 and *BDNF* rs6265 lead serotonin levels out of optimal range [46]. On a neurological level, serotonin is mainly expressed in the raphe nuclei, which extend to brain regions such as the hippocampus, amygdala, prefrontal cortex, and anterior cingulate – brain regions commonly reported to show altered activity in FND [3,47]. Impairments of serotonin function were not only found to affect the development of macroscale anatomical connectivity [48], but were also found to increase the amygdala's response to emotional stimuli, representing a potential modulatory effect [49]. Likewise in FND, altered amygdalar connectivity to motor regions has been reported [50], suggesting to reflect increased arousal to emotional stress, which further modulates motor preparation and thus might represent a neural correlate of physical symptom presentation in FND. In addition, history of childhood physical abuse was linked to cortico-limbic brain network alterations in regions which in situ showed an overlap with high expression of *BDNF* [6]. These findings in FND firstly linked alterations in brain circuits responsible for emotion regulation to *BDNF* expression, suggesting a mediating role in trauma-related neuroplastic brain changes [6], for which we further suggest an effect on clinical outcome in FND. In summary, it is suggested that particular genetic combinations of *TPH1* (rs1800532), *TPH2* (rs4570625) and *BDNF* (rs1491850) might contribute to the maintenance of serotonin levels within an optimal range, which is especially relevant in signalling pathways regulating the neuroplastic restoration of neuronal circuits involved in the pathophysiology of several neuropsychiatric disorders [43], and thus in clinical outcome in FND patients. However, while patients reported in average around 4.75 years of illness duration, around 31 patients showed a significant improvement after eight months following their therapy as usual, and apart from potential genetic effects also psychosocial factors might come in play. The differences in symptom manifestation may be attributed to the varying influences of diverse psychosocial factors as well as biological predispositions to FND in the form of a stress-diathesis model [11], in which a genetic vulnerability may moderate the relationship between experience of adverse life events and symptom severity.

### 4.3. Limitations

It should be considered that other genes and SNPs not assessed in the present study probably interact with the biological scenario presented. Particularly, our findings support the hypothesis that FND would only be expressed if the global effect of multiple genetic variants results in a failure of the system to maintain homeostasis in the face of sustained environmental challenge [9]. Even though our sample size is as big as in the work of Spagnolo et al. [9], it is not sufficient for a genetic study [51], and thus requires a replication in a much larger sample, alongside different subtypes of FND symptoms. Likewise, the association we observed reached only nominal significance without adjustment for multiple comparisons (i.e., number of SNPs), which increases the likelihood of false positive/negative findings. Similarly, our MDR analysis relies on cross-validation to assess model performance instead of an independent test sample. While cross-validation is a robust method for estimating predictive performance, it may not fully represent the model's generalizability to new datasets. Additionally, the statistical significance derived from balanced accuracy and permutation testing

should be interpreted with caution, as it is based on internal validation. Future studies should validate these findings with independent datasets to ensure the robustness and generalizability of the results. Moreover, the candidate gene approach used in this study is inherently limited by its potential for high false positive rates and a poor replication track record, which should be considered when interpreting our findings. Additionally, this approach focuses on pre-selected genes, potentially overlooking other relevant genetic variants or pathways, thereby providing an incomplete picture of the genetic basis of FND. Furthermore, the serotonergic pathway and potential effects of genetic variations has most commonly been studied in the framework of depression [32] and our results might have been partially driven by the fact that depression and anxiety represent a frequent comorbidity for FND [52]. However, all our models were corrected for the concomitant effects of depression and anxiety, suggesting a specific role of the serotonergic pathway in the development and maintenance of FND itself. Lastly, there might be a selection bias in the subjects that agreed to the follow-up visit, as they showed lower anxiety values in comparison to those subjects who did not agree or were lost to the follow-up visit.

## 5. Conclusion

In summary, we identified a significant association of *TPH1* (rs1800532) with symptom severity. Moreover, a significant gene-gene interaction between *TPH2* (rs4570625) and *OXTR* (rs2254298) might be implicated in the development and maintenance of functional neurological symptoms. Furthermore, *TPH1* was associated with clinical outcome for which also a synergistic effect of *TPH2* and *BDNF* was identified, suggesting an effect on clinical outcome potentially mediated through neuronal plasticity. Taken together, these preliminary results point towards a significant involvement of the serotonergic system in FND but needs to be validated within a greater study sample specifically focusing on the diverse subtypes. Thus, FND might be the result of the interaction of several genetic risk variants with a probable small individual effect in combination with adverse environmental conditions. In summary, while genetic factors might play an important (potentially moderating) role in the development and course of FND, other factors are also important contributors and should not be out of focus.

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## CRediT authorship contribution statement

**Samantha Weber:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lucía Trinidad Rey Álvarez:** Writing – review & editing, Writing – original draft. **Juan Ansede-Bermejo:** Methodology, Formal analysis, Data curation. **Raquel Cruz:** Methodology, Formal analysis. **Álvaro del Real:** Methodology, Formal analysis. **Janine Bühler:** Data curation. **Ángel Carracedo:** Supervision, Resources, Methodology. **Selma Aybek:** Writing – review & editing, Supervision, Resources, Funding acquisition.

## Declaration of competing interest

The authors have no competing interests to report.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2024.111909.

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