Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease

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ABSTRACT

Objectives: Impulse control disorders (ICD) are commonly associated with dopamine replacement therapy (DRT) in Parkinson's disease (PD) patients. Our aims were to estimate ICD heritability, and to predict ICD by a candidate genetic multivariable panel in PD patients.

Methods: Data from de novo PD patients, drug-naïve, and free of ICD behaviour at baseline were obtained from the Parkinson's Progression Markers Initiative cohort. Incident ICD behaviour was defined as positive score on the Questionnaire for Impulsive-Compulsive Disorders in PD. ICD heritability was estimated by restricted maximum likelihood analysis on whole exome sequencing data. Thirteen candidate variants were selected from the *DRD2*, *DRD3*, *DAT1*, *COMT*, *DDC*, *GRIN2B*, *ADRA2C*, *SERT*, *TPH2*, *HTR2A*, *OPRK1*, and *OPRM1* genes. ICD prediction was evaluated by the area under the curve (AUC) of receiver operating characteristic (ROC) curves.

Results: Among 276 PD patients included in the analysis, 86% started DRT, 40% dopamine agonists (DA), 19% reported incident ICD behaviour during follow-up. We found heritability of this symptom to be 57%. Adding genotypes from the 13 candidate variants significantly increased ICD predictability (AUC=76%, 95%CI [70-83%]) compared to prediction based on clinical variables only (AUC=65%, 95%CI [58-73%], p=0.002). The clinical-genetic prediction model reached highest accuracy in patients initiating DA therapy (AUC=87%, 95%CI [80-93%]). *OPRK1*, *HTR2A,* and *DDC* genotypes were the strongest genetic predictive factors.

Conclusion: Our results show that adding a candidate genetic panel increases ICD predictability suggesting potential for developing clinical-genetic models to identify PD patients at increased risk of ICD development and guide DRT management.

INTRODUCTION

Impulse control disorders (ICD) and related behaviours are defined by failure to resist an impulse to perform a self-rewarding act that will cause longer-term harm and are referred to as "behavioural addictions".[1] In Parkinson disease, ICDs are associated with dopamine replacement therapy (DRT). ICDs (either formal diagnosis or symptoms) are estimated to occur in 14-40% of Parkinson's disease (PD) patients once DRT, in particular dopamine agonist (DA) treatment, is initiated, greatly exceeding the prevalence in the general population.[2-4] Commonly reported presentations in PD patients include compulsive gambling, eating, buying, and sexual behaviours , and multiple co-morbid ICDs are common. [5 6] These behavioural disorders represent an important public health problem because of their potential socioeconomic and legal impact, leading to reconsideration of the benefit/risk ratio of initiating DA therapy.[7 8]

However, not all treated PD patients develop ICDs, suggesting a shared clinical and neurobiological contribution to individual ICD susceptibility. Identification of such predictive factors may allow a tailored therapeutic approach in subpopulations at risk. Clinical features that have been associated with ICD in PD in cross-sectional studies include depression, anxiety, a personal or family history of alcohol abuse or gambling, increased impulsivity, novelty-seeking traits, younger age, early PD onset, unmarried status, and past or current smoking.[6-12]

In the general population, family, adoption, and twin studies have provided evidence that genetic factors might contribute up to 60% of the variance in the risk for substance use disorders and pathological gambling.[13 14] So far, ICD heritability has not been studied in the PD population. ICDs and substance use disorders might share common neurobiological mechanisms with involvement of monoaminergic, glutamatergic, and opioid neurotransmitter systems.[15 16] Several genetic studies reported that single genetic variants involved in these pathways are associated with addiction and impulsivity in non-PD cohorts.[17 18] Only four genetic association studies have been published on ICD in PD patients so far.[19-22]

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These studies were of cross-sectional design and included a relatively small number of patients.

We utilized a large, longitudinal cohort of de novo PD patients with extensive clinical and genetic data. Our main objectives were to first assess ICD heritability in PD, and then to evaluate the contribution of a preselected panel of candidate gene variants in predicting ICD when added to clinical variables.

PATIENTS AND METHODS

Study design

The Parkinson's Progression Markers Initiative (PPMI) is an ongoing longitudinal multicenter international study designed to identify biomarkers of PD progression in de novo and drug-naïve (at baseline) PD patients. Data acquisition follows standardized protocols; PD diagnosis is made following established diagnostic criteria and confirmed by reduced striatal dopamine transporter (DAT) binding at enrollment. PPMI is a public-private partnership, sponsored by The Michael J. Fox Foundation. Details on study design, study goals and funding are described on the PPMI website (http://www.ppmi-info.org). The PPMI study was conducted in accordance with Good Clinical Practice and any applicable national and local regulations. All patients signed an informed consent before their participation in the PPMI study.

The PPMI database (www.ppmi-info.org/data) provided all clinical and genetic information for our analysis; download was performed December 16, 2014 for clinical information, March 19, 2015 for genetic data, PD medication data was updated March 26, 2015.

Genetic data included the NeuroX genotyping array, containing a selection of 292 313 variants, specifically designed for neurological disease studies, as well as whole exome sequencing. The methodology was previously published and its usage in PPMI described on the PPMI website.[23-26]

Participants and clinical measures

For our study, we included only PD patients who screened negative for ICD behaviour at baseline and had available genetic data on both NeuroX and exomes. Incident ICD behavior was defined as a positive score for any symptom (i.e., compulsive gambling, sex, buying, eating, hobbyism, simple motor activities or walkabout) of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)-short form at any annual post-baseline visit. The QUIP is a validated screening tool to assess ICD behaviours, related compulsive behaviours and compulsive medication use in PD patients.[27]

Participants were considered to be on DRT (i.e., levodopa, DA, amantadine, or monoamine oxidase-B inhibitor) from the first time it was recorded at an annual study visit. Subjects lacking either QUIP or DRT data were excluded from analysis.

Candidate gene and SNP selection

We identified all frequent (MAF > 0.2) single nucleotide polymorphisms (SNPs) on exome sequencing and NeuroX genotyping data, which we then extracted using plink software (plink, pngu.mgh.harvard.edu/~purcell/plink/).[28] We selected 15 autosomal candidate genes for their involvement in monoaminergic systems or based on published ICD literature: *SLC6A3*, *DRD2*, *DRD3, DRD4, DDC, TPH2, HTR1A, HTR2A, HTR2C, SLC6A4*, *COMT, OPRK1, OPRM1, GRIN2B* and *ADRA2C*. For each candidate gene, all variants present on the NeuroX or exome data within its genomic coordinates were determined. We then chose a maximum of two SNPs per gene to prevent overfitting in the multiple regression model. SNPs were selected following predefined selection criteria: (1) we looked for variants that have been associated with ICD or addictive behaviour in literature;[17 18] (2) if none was present on either NeuroX or exome sequencing data, we sought variants in linkage disequilibrium with these SNPs (D'>0.8); (3) if not available we chose among the frequent SNPs (MAF>0.2) present on the gene region; (4) for each step we filtered the variants based on their functional category, with preferential inclusion as follows: missense > coding synonymous > UTR'3/UTR'5 > Intron > the most frequent SNP of the preferred category.

Statistical analysis

Heritability of ICD behaviour was estimated performing restricted maximum likelihood (REML) analysis, using Genome-wide Complex Trait Analysis (GCTA) software, http://www.complextraitgenomics.com/software/gcta). We determined variance of incident ICD behaviour explained by autosome-wide SNPs, while taking into account predefined clinical covariates known to be associated with ICD.[5] Clinical variables selected were age, sex, PD treatment (no treatment, DA treatment, other DRT), and duration of follow-up in the study.

Incident ICD behaviour predictability was estimated with receiver operating characteristic (ROC) curves. To assess whether inclusion of genotype information would improve predictability of ICD behaviour incidence, ROC curves were plotted with the preselected clinical variables only, and then with candidate gene information added. Area under the curves (AUCs) were compared using DeLong's test for two correlated ROC curves.[29] Hosmer and Lemeshow goodness-of-fit test was performed to validate our logistic regression model.

Adjusted single factors associated with ICD incidence were assessed using logistic regression models, with variable selection carried out in a backwards stepwise fashion based on the Akaike information criterion (AIC). Because DA treatment is the DRT most strongly associated with ICD, a similar secondary enriched analysis was performed on the subgroup of patients on DA treatment versus no DRT at all. No correction for multiple comparisons was performed due to the exploratory nature of the study.

RESULTS

Patient characteristics

Baseline clinical and genetic data were available for 276 PD patients, 183 men (66.3%), 96.4% Caucasian, with a mean age of 65.04 [SD 9.6] years, and a mean formal education of 15.58 [SD 3.0] years (**Table 1**). At baseline, mean disease duration was 6.31 [SD 6.3] months, and the mean Unified Parkinson's Disease Rating Scale part III score 21.46 [SD

9.0]. Of this cohort, follow-up visits occurred for 98% (n=270) at year 1, 84% (n=232) at year 2, and 38% (n=106) at year 3. Across the entire PPMI study, the retention rate at the time of analysis was 92%, so nearly all participants without year 2 or 3 data remain active study participants, but have not yet reached these later time points. In our cohort, 238 patients (86%) started DRT during follow-up, including 111 (40%) patients on a DA. Fifty-two patients (19%) reported incident ICD behaviour during follow-up.

Table 1: Baseline characteristics

N	276
Sex, % male (Male: Female)	66.3% (183: 93)
Race, % white (n)	96.4% (266)
Age, years	65.04 [9.6]
Formal education, years	15.58 [3.0]
Montreal Cognitive Assessment score	27·24 [2.3]
Duration of PD, months	6·31 [6.3]
UPDRS part III score	21.46 [9.0]
Duration of follow-up, years	2.20 [0.8]

Legend: Values are means [standard deviation], n= number.

Candidate gene selection

We identified at least one frequent polymorphism in 12 of the 15 candidate genes; for the *DRD4* and *HTR1A* gene, no frequent variant was found, so these genes were not included in the analysis. For the *DDC* gene we included a second variant, as no single SNP has been implicated in ICD or addictive behaviours so far, no frequent SNP in the coding region was found, and the gene is large in size (107 020 bp). Thus, our final set of candidate variants

consisted of 13 SNPs in 12 candidate genes. Allele and genotype distributions of all 13 variants respected Hardy-Weinberg equilibrium (**Table 2**).

Table 2: Characteristics of the selected genetic variants

Gene	Variant	Alleles	Location in gene	MAF
SLC6A3 (DAT1)	rs27072	C/T	UTR'3	T=0.205
DRD2	rs1800497	G/A	Exon, missense	A=0.326
DRD3	rs6280	C/T	Exon, missense	C=0.486
GRIN2B	rs7301328	C/G	Exon, synonymous	C=0.442
HTR2A	rs6313	G/A	Exon, synonymous	A=0.441
TPH2	rs7305115	A/G	Exon, synonymous	A=0.458
SLC6A4 (SERT)	rs7224199	G/T	UTR'3	G=0.419
ADRA2C	rs76337672	C/G	UTR'3	C=0.422
DDC	rs3837091 (DIV)	-/CTCT	UTR'5	-=0.293
DDC	rs1451375	A/C	Intron	A=0.346
COMT	rs4680	A/G	Exon, missense	A=0.369
OPRM1	rs1799971	A/G	Exon, missense	G=0.223
OPRK1	rs702764	C/T	Exon, synonymous	C=0.245

Legend: MAF = minor allele frequency as reported in the dbSNP database, DIV = deletion/insertion variation, UTR'3 = three prime untranslated region, UTR'5 = five prime untranslated region.

ICD heritability

Variance of ICD incidence explained by all frequent autosomal SNPs from whole exome sequencing (MAF >0.2, 44,504 SNPs) was estimated to be 57% [SE ±39.8%].

ICD prediction based on clinical and genetic variables

ROC curves plotted with clinical variables (sex, age, PD treatment, and length of follow-up) with or without genetic variables are displayed in **Figure 1**. The AUC was 0.65 [95%CI: 0.58-

0.73] when only clinical variables were used in the model, and increased by 11% to 0.76 [95%CI: 0.70-0.83] (P=0.002, DeLong's test) when adding genotype data for the 13 SNPs. The subgroup analysis of the 149 patients either initiating DA treatment or not on DRT during follow-up revealed even greater ICD predictability with genetic data added to the model compared to clinical variables alone. When genotype data was added, AUC increased significantly by 16% (from 0.71 [95%CI: 0.62-0.8] to 0.87 [95%CI: 0.80-0.93], p<0.001) (**Figure 2**).

Stepwise regression

In order to identify individual factors that contribute to ICD predictability, we performed a backward stepwise regression. DRT, age and the length of follow-up were significant clinical predictors. The significant genetic predictors were *TPH2* and *OPRK1* genotypes.

The same analysis was performed in the subset of patients either initiating DA or no DRT during follow-up, revealing age, male sex, DRT and *ADRA2C*, *DRD2*, *DDC*, *HTR2A* and *OPRK1* genotypes as significant predictors of incident ICD behaviour.

Independent factor associations

The significant variables from the stepwise regression were used in multivariate logistic regression, which showed significant associations of single genetic variants with ICD behaviour incidence (**Table 3**). The heterozygous genotype of *OPRK1* was significantly associated with incident ICD behaviour (P=0.03), suggesting a dominant effect of the minor allele C. There was a suggestion of an association with the minor homozygous genotype of the *TPH2* polymorphism (P=0.07) and for the duration of follow-up (P=0.07). In addition, ICD behaviours occurred at increased frequency in patients on DA compared with untreated patients (P=0.04), whereas no significant difference was found for patients using DRT other than DA compared with untreated patients (P=0.13).

Table 3: Single factor associations with ICD incidence in the multivariable non-linear model, whole population

Factor	Multivariable P-value
(Intercept)	0.217
OPRK1: rs702764: TC genotype	0.033
OPRK1: rs702764: CC genotype	0.989
TPH2: rs7305115: GA genotype	0.819
TPH2: rs7305115: AA genotype	0.077
Dopamine agonist use	0.036
Other DRT	0.125
Age	0.125
Duration of follow-up	0.072

Legend: Sets of variables were determined using stepwise regression. P-values for each variable were adjusted for the other covariates. DRT = dopamine replacement therapy.

Multivariate logistic regression in the sub-cohort of patients either treated with a DA or no DRT during follow-up revealed that patients who started DA treatment were more likely to develop ICD behaviours compared with untreated patients (P=0.001) (**Table 4**). Male sex was significantly associated with ICD behaviour incidence (P=0.01). Heterozygous genotype of the *OPRK1* and the *HTR2A* variants were significantly associated with incident ICD behaviours (P=0.04, and P=0.008). Significant associations were also found for the heterozygous and minor homozygous genotype of the rs3837091 *DDC* polymorphism (P=0.01, and P=0.04), as well as the minor homozygous genotype of the rs1451375 *DDC* SNP (P=0.04). No significant association was found for the *ADRA2C* and *DRD2* variants.

Table 4

Single factor associations with ICD incidence in the multivariable non-linear model, patients taking DA only

Factor	Multivariable P-value
(Intercept)	0.578
OPRK1: rs702764: TC genotype	0.038
OPRK1: rs702764: CC genotype	0.997
HTR2A: rs6313: GA genotype	0.008
HTR2A: rs6313: AA genotype	0.456
DDC: rs383709: -/AGAG genotype	0.01
DDC: rs3837091: -/- genotype	0.043
DDC: rs1451375: CA genotype	0.122
DDC: rs1451375: AA genotype	0.037
ADRA2C: rs76337672: GC genotype	0.705
ADRA2C: rs76337672: CC genotype	0.995
DRD2: rs1800497: GA genotype	0.655
DRD2: rs1800497: AA genotype	0.993
Age	0.071
Sex	0.014
Dopamine agonist use	0.001

Legend: Sets of variables were determined using stepwise regression. P-values for each variable were adjusted for the other covariates. Subgroup analysis was performed on 149 patients who either were on DA treatment or did not receive DRT during follow-up. DA = dopamine agonist, DRT = dopamine replacement therapy.

DISCUSSION

This is the first study to evaluate ICD heritability in a prospective cohort of de novo PD patients. Incident ICD behaviour was common in this cohort, with a cumulative frequency of 19%, and initiation of DA treatment significantly increased risk compared with other DRT classes. Though the majority of the literature addresses ICD prevalence rather than incidence, the rates in our study are within the range reported in cross-sectional studies.[2-4] Based on whole exome data, we found common genetic variants to account for more than half (57%) of the variance of ICD incidence in PD patients. This finding is comparable to previous estimations on heritability for substance addiction and pathological gambling in the general population.[13 14]

A broad genetic screening technique such as whole exome sequencing may be important in stratifying PD patients' ICD risk, since the contribution of single genetic variants to ICD susceptibility may be small, multiple gene interactions may play a role, and several neurotransmitter systems may contribute to ICD pathogenesis.[30] By selecting a multi-polymorphism profile comprised of genes implicated in monoaminergic, glutamatergic, and opioid signalling pathways we found a substantial 11-16% increase in ICD behaviour predictability compared to examining clinical variables alone. Incident ICD behaviour predictability was particularly strengthened in patients initiating DA treatment versus those Parkinson's disease patients remaining untreated during follow-up, with an AUC approaching 90%. The latter group controlled for the suboptimal specificity of the QUIP (i.e., the relative high potential for a false-positive incident QUIP in a patient who has not yet initiated DRT) and therefore supports clinical relevance of this finding. This is the first proof-of-concept study demonstrating that clinical-genetic modelling could provide clinically meaningful risk stratification and lead to personalized therapy for PD patients once validated in independent prospective studies.

Our model suggests that genetic variants in several neurotransmitter systems that have been previously associated with behavioural addictions may contribute to ICD risk in PD. Dopamine, serotonin and norepinephrine genes have been shown to contribute to ICD

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predisposition in the general population.[16 30] In addition, considerable evidence supports the importance of glutamatergic and opioid transmitter systems for behaviour and impulsivity regulation.[15 16] To date, evaluation of ICD susceptibility in PD has focused on independent associations of single variants, including polymorphisms of the *DRD1-5*, *SLC6A4* (*SERT1*), *HTR2A*, *GRIN2B*, *COMT* and *SLC6A3* (*DAT1*) genes. We extended the spectrum of monoaminergic ICD candidate genes by adding the *DDC* gene (which encodes for AADC (aromatic l-amino acid decarboxylase), an enzyme involved in dopamine and serotonin biosynthesis) and the *TPH2* gene (which encodes for the rate-limiting enzyme of serotonin synthesis). To our knowledge, this was the first study to also evaluate genes involved in noradrenergic (*ADRA2C*) and opioid (*OPRM1* and *ORPK1*) signalling in PD ICD. Alpha-2 adrenergic receptors are expressed in the caudate and accumbens nuclei as well as in the hippocampus and cerebral cortex, and are implicated in the regulation of behavioural responses.[31] The endogenous opioid system mediates affect, motivation, as well as reactivity to stress and reward by modulating the mesolimbic dopamine pathway. Mesolimbic neurons may either be excited by μ-opioid receptor activation or inhibited by either μ-opioid or κ-opioid receptors depending on their target projections.[15] Both, particularly the μ-opioid receptor, have been extensively studied for their implication in substance addiction with some contradictory results.[15 32 33]

In the entire cohort our multivariate model revealed the *OPRK1* polymorphism rs702764 significantly predicted incident ICD behaviour. This variant has previously been reported to be part of a risk haplotype accounting for higher alcohol use and withdrawal symptoms in patients with methadone maintenance.[34] However, in another study, no association was found with heroin and alcohol addiction.[35] Interestingly, a recent randomized, placebo-controlled clinical trial showed that the opioid receptor antagonist naltrexone decreases ICD symptom severity in PD patients with ICD.[36]

In the sub-cohort of patients initiating DA therapy, multivariable analysis showed independent associations of the *OPRK1, DDC* and *HTR2A* variants with new-onset ICD behaviours. The serotonin 2A receptor has been implicated in the modulation of drug

addiction, and specifically the functional *HTR2A* rs6313 variant has been reported to predispose for impulsivity and addiction in the general population as well as ICD in PD patients.[20]

This is the first study reporting an association of *DDC* variants with ICD in PD. *DDC* polymorphisms/haplotypes have been associated with impulsivity and addiction in the general population.[37-39] The *DDC* rs3837091 promoter deletion polymorphism has recently been reported to influence the motor response to levodopa.[40] The discrepancy in genetic predictors between the whole cohort and the DA-treated subgroup may be due to medication-specific drug-gene interactions that mediate the interplay between these neurotransmitter systems and dopamine neurotransmission.

To date, polymorphisms of the *DRD1*, *DRD2*, *DRD3*, *HTR2A* and *GRIN2B* genes have been associated with ICD in PD patients.[19-22] None of these genes sustained stepwise regression in our cohort, suggesting that their independent contribution may be too low to be detected. Discrepancy between our findings and previous reports may also be due to differences in study design (e.g., cross-sectional versus prospective, method of ICD behaviour assessment and cohort characteristics).

Because our cohort consisted of early PD patients, disease duration was relatively short, and the length and dose of DRT exposure would be expected to be low overall, which might have contributed to differences in genetic susceptibility to ICD. Indeed, *5HTR2A* polymorphism was found to increased ICD risk only in patients receiving low LEDD.[20] Certain genetic variants might enhance ICD risk in the absence of other clinical risk factors (e.g., DA use, higher LEDD), while other variants might increase ICD risk only under specific treatments (e.g., DA treatment). Ethnic background also needs to be considered, and our results must be confirmed across more diverse ethnicities. The only previous study in PD patients with European ancestry showed no significant association with the *DRD2* and *COMT* genes, similar to our findings.[21]

In terms of study limitations, our candidate selection of SNPs analysed in our study may have been too restrictive and the global genetic effect of DRT on ICD behaviour in PD

patients may be further elucidated by future genome-wide gene-drug interaction studies in larger cohorts. Another limitation was assessment of ICD behaviours by the QUIP, which might have led to a falsely high incidence rate due to the high sensitivity and lower specificity of the QUIP. Formal ICD diagnostic criteria should be applied in future studies. In addition, we were not able to assess the impact of DRT doses. Different dopamine agonists might have differential risks for ICD development, as recently shown for subcutaneous forms.[41] Because the sample size was limited, dopamine agonists were considered as a class in our analysis. Larger cohort of patients will be needed to investigate potential drug specific genetic risk factors for ICD behaviours. Although PPMI is the largest prospective cohort of de novo PD patients to date, our proposed genetic algorithm must be replicated and refined in similar longitudinal cohorts before it may be translated into clinical practice. Then, a "personalized medicine" approach may be develop for the management of PD patients based on their genetic profile. For instance, patients at significantly increased risk for ICD development based on their demographic, clinical, and genetic profile might not be initiated on a dopamine agonist, instead being treated with other antiparkinsonian medications.

In summary, we found incident ICD behaviours to have a substantial hereditability in early PD. A 13-SNP genetic panel significantly increased ICD predictability, leading to a predictive model reaching clinically relevant accuracy. We provide supportive evidence that the *HTR2A* variant rs6313 is an independent risk factor for ICD development, and for the first time report that *OPRK1* and *DDC* polymorphisms are associated with incident ICD behaviours in PD. Our results suggest there may be premorbid genetically determined neurobiological risk factors for ICD in PD, although it is unlikely that a single genetic variant or genetic variation in a single neurotransmitter system will be sufficient to predict this complex condition. Additional studies are needed to replicate these findings before applying them to clinical practice, to further disentangle the relationships among clinical, pharmacologic and genetic risk factors for ICD development in PD, and to determine the functional relevance of genetic risk factors.

CONFLICT OF INTEREST

JK reports no conflict of interest. KS has received an unrestricted educational grant from Medtronic Inc. DW has received research funding or support from Michael J. Fox Foundation for Parkinson's Research, National Institutes of Health (NINDS), Novartis Pharmaceuticals, Department of Veterans Affairs, Avid Radiopharmaceuticals, Alzheimer's Disease Cooperative Study, and the International Parkinson and Movement Disorder Society; honoraria from AbbVie, Acadia, Biotie, Clintrex LLC, Otsuka, Teva Pharmaceuticals, UCB, and the CHDI Foundation; license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS; royalties from Wolters Kluweland; and fees for legal consultation for lawsuit related to antipsychotic prescribing in a patient with Parkinson's disease. VG reports grants from "Investissements d'Avenir" ANR-10-IAIHU-06 during the conduct of the study. MAN reports no conflict of interest. FC reports no conflict of interest. IM reports grants from "Investissements d'Avenir" ANR-10-IAIHU-06 during the conduct of the study. AB reports no conflict of interest. ABS reports no conflict of interest. JCC reports grants from the program "Investissements d'Avenir" ANR-10-IAIHU-06 during the conduct of the study. JCC reports research grants from the French Ministry of Health, the Michael J. Fox Foundation, Ipsen,

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FIGURE LEGENDS

Figure 1

ROC curves for prediction of ICD incidence in the whole population.

The red ROC curve was plotted with clinical variables only (age, gender, DRT and duration of follow-up period). The blue ROC curve was plotted with clinical and genetic variables combined. The genetic variables consisted of genotype data on 13 preselected SNPs. P-value refers to AUC comparison of the two curves.

Figure 2

ROC curves for prediction of ICD incidence in patients using dopamine agonists.

The red ROC curve was plotted with clinical variables only (age, gender, DRT and duration of follow-up period). The blue ROC curve was plotted with clinical and genetic variables combined. The genetic variables consisted of genotype data on 13 preselected SNPs. P-value refers to AUC comparison of the two curves.
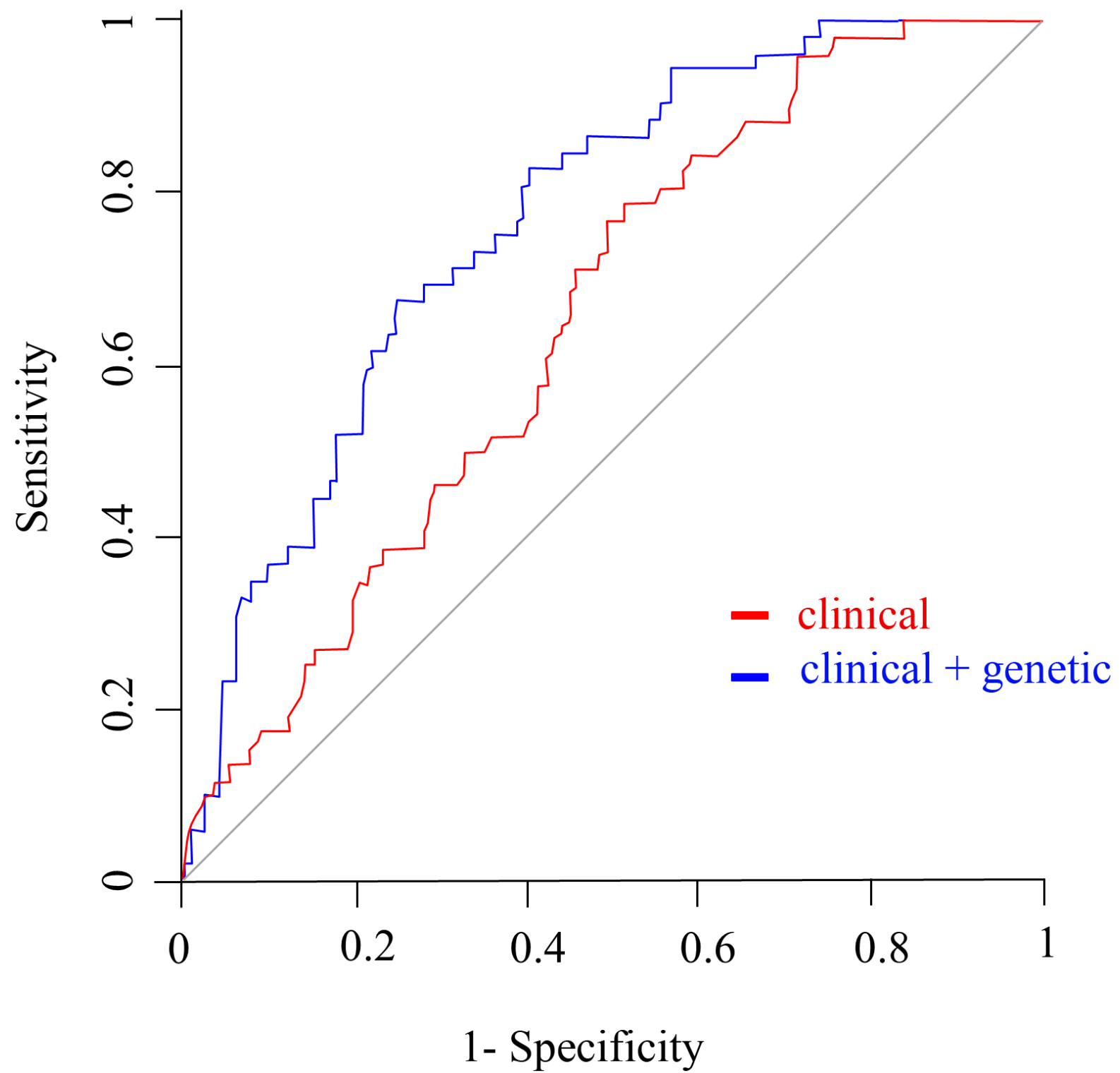
Figure 1

Figure 2