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Genetic risk underlying psychiatric and cognitive symptoms in Huntington's Disease

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Abstract

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expanded CAG repeat in the HTT gene. It is diagnosed following a standardized exam of motor control and often presents with cognitive decline and psychiatric signs and symptoms. Recent studies have detected genetic loci modifying the age at onset of motor symptoms in HD, but the genetic factors influencing psychiatric presentations are as yet unknown. There is, however, evidence that phenotypic expression in monogenic neurodevelopmental disorders is affected by the same variants as in the general population. We tested this hypothesis in HD by constructing polygenic risk scores from large genome-wide association studies of psychiatric and neurodegenerative disorders, and of intelligence, and testing for correlation with the presence of psychiatric and cognitive symptoms in a large sample (n=5160) of HD patients. Schizophrenia polygenic risk score was significantly associated with increased risk of psychiatric symptoms in HD, including psychosis, and independent associations were also observed between psychiatric symptoms and risk scores for bipolar disorder and major depression. Interestingly, cognitive impairment and apathy were associated with reduced polygenic risk score for intelligence, suggesting a genetic background distinct from other psychiatric symptoms in HD. Notably, no associations were observed between psychiatric and cognitive symptoms in HD and polygenic risk scores in other major neurodegenerative disorders. This may reflect susceptibility to neurodegeneration of specific neuronal subsets in each neurodegenerative disorder, but susceptibility to psychiatric symptoms in surviving cells is influenced by the psychiatric polygenic risk.

Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expanded CAG repeat in *HTT*. Diagnosis is typically made via a movement disorder, but nearly all participants experience progressive cognitive decline, and many exhibit a variety of behavioural and psychiatric symptoms (1). Depression, irritability, obsessive and compulsive symptoms, apathy and psychosis all occur at rates higher than seen in the non-HD population, though they are not universal in HD (2). Psychiatric symptoms are often present before motor symptoms become manifest. Age at motor onset of HD is determined both by the length of the CAG repeat tract in *HTT* and by other genetic variants in the genome (3–5). Despite the fact that age at motor onset measures only one specific facet of the pathological process (1), it has been widely used to identify genetic modifiers in HD whilst genetic influences on behavioural and neuropsychiatric symptoms in HD have not been systematically investigated. Small studies have shown familial aggregation of psychosis in HD (6,7) with weak evidence for the influence of specific candidate genes (8).

Psychiatric disorders are known to have a sizeable and overlapping polygenic component (9). Common genetic variation contributes to the risk of developing schizophrenia (SCZ) (10), bipolar disorder (BPD) (11), major depressive disorder (MDD) (12) and attention deficit hyperactivity disorder (ADHD) (13). There is significant shared heritability between the psychiatric disorders, with schizophrenia having a greater than 0.5 genetic correlation with bipolar disorder and lower but still significant genetic correlation with ADHD, MDD and obsessive compulsive disorder (OCD) (9), implicating substantial shared genetic risk for these diseases.

Increased general intelligence (*g*) – a measure of cognitive function - has been shown to be genetically correlated with reduced risk of Alzheimer's disease (AD), ADHD and schizophrenia (14). As in HD, there are substantially increased levels of psychiatric symptoms in many neurological diseases. For instance 50% of those with AD (15), and up to 75% of those with Parkinson's disease

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(PD) develop psychotic symptoms, though in PD these are partly caused by medication to control the movement disorder (16,17). In dementia with Lewy bodies visual hallucinations are a core clinical feature seen in 80% of patients (18). AD with psychosis is heritable (19,20), though increasing polygenic risk score for schizophrenia was associated with reduced risk of psychosis in PD and AD (21).

Given the increased frequency of neuropsychiatric and cognitive symptoms in HD, it is of interest to test for genetic overlap of these symptoms with psychiatric and neurodegenerative disorders and intelligence. This was done by constructing polygenic risk scores using the latest available genome-wide association studies for these disorders and testing these for correlation with the presence of neuropsychiatric and cognitive symptoms in HD.

Materials & Methods

HD participants and phenotypes

The HD participants in this analysis were part of the European REGISTRY study (22) or its successor, the international Enroll-HD (23) observational study of HD. REGISTRY was a multisite, prospective, observational study, which collected phenotypic data (2003–13) for more than 13000 participants, mostly HD gene carriers with manifest disease. Enroll-HD is an expanded and modified version of the REGISTRY study and is international: to date it has over 16000 participants (some of whom rolled over from REGISTRY) from 19 nations. All experiments were performed in accordance with the Declaration of Helsinki, ethical approval for the REGISTRY and Enroll-HD studies including written informed consent of all participants was obtained. This study was approved by Cardiff University School of Medicine Research Ethics Committee.

There were 6278 individuals with manifest HD defined by motor onset from REGISTRY (n=4986) and Enroll-HD (n=1292) with appropriate quality-controlled genome-wide association study (GWAS) data as described in (5). We examined seven symptoms: depression, irritability, psychosis, apathy, violent/aggressive behaviour, perseverative/obsessive behaviour and cognitive impairment, from the clinical characteristics questionnaire (CCQ) in REGISTRY and Enroll-HD. The clinical characteristics questionnaire asks if a sign or symptom has ever been experienced by a subject, (see Supplementary Information Appendix A). At least one CCQ symptom endorsement (positive or negative) was recorded in 5854 participants (4563 REGISTRY, 1291 Enroll-HD). We removed 133 individuals with a comorbid diagnosis of bipolar disorder, schizophrenia, schizotypy or schizoaffective disorder (since these will by definition share risk genes for psychiatric disorders independently of their HD status). We also removed one member of each pair of first or second degree relatives (IBD>0.25) to minimise the correlation between individuals due to cryptic relatedness. 561 individuals were removed in this step, leaving 5160 participants in the final analysis (**Supplementary Figure 1**).

Genetic analysis

For each individual in the HD dataset, their genetic risk for each psychiatric/neurodegenerative disorder was captured by a polygenic risk score (PRS) (24). A PRS is defined as the sum of the number of minor alleles across a set of SNPs, each weighted by the corresponding risk of that allele for the psychiatric/neurodegenerative disorder observed in a “training” GWAS. The set of SNPs used to calculate the PRS was chosen to be present in both the training GWAS and the HD dataset, to be in approximate linkage equilibrium, and to capture as much of the association signal in the training

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GWAS as possible. Following the procedure outlined by the Psychiatric Genomics Consortium (10), this was achieved by taking the most significant SNP in the training GWAS, removing all SNPs within 500kb that are in linkage disequilibrium (r^2>0.1) with it, then moving to the next most significant remaining SNP and repeating the process. Analysis was restricted to SNPs that were common (minor allele frequency >0.01) and well imputed (r^2 between allele dosages and the unknown true genotypes >0.9) in the HD dataset and (where this information was available) in the training GWAS. SNPs were selected for inclusion into the PRS by applying criteria to their p-values in the training set. Since the optimal criterion was not known *a priori,* we applied six different p-value cutoffs (p<0.0001, p<0.001, p<0.01, p<0.05, p<0.5, p<1). Effects of population stratification were removed by regressing the PRS on 20 principal components. The residuals from this regression were standardised, to enable comparison of effect sizes between p-value cutoffs.

Nine large publically available sets of GWAS summary statistics were used for training (**Supplementary Table 1**). These comprised six psychiatric disorders from the Psychiatric Genomics Consortium: schizophrenia, bipolar disorder, major depression, ADHD, autism spectrum disorder (ASD) and obsessive compulsive disorder (OCD) (9–13,25), two neurodegenerative disorders (the International Genomics of Alzheimer's Project (IGAP) GWAS of late-onset Alzheimer's disease (26), and the International Parkinson Disease Genomics Consortium (IPDGC) Parkinson's GWAS) (27,28) and a large GWAS of *g*, a measure of general intelligence (14). Note that the Major histocompatibility complex (MHC) region was removed from the schizophrenia GWAS due to a strong schizophrenia signal and long-range linkage disequilibrium potentially biasing the PRS (10). Summary statistics for the Psychiatric Genomics Consortium GWAS are available from https://www.med.unc.edu/pgc/results-and-downloads, those for the IGAP and intelligence GWAS from https://www.ebi.ac.uk/gwas/downloads/summary-statistics, and the IPDGC GWAS (omitting 23 and Me samples) from https://drive.google.com/drive/folders/10bGj6HfAXgl-JslpI9ZJIL_JIgZyktxn.

We tested for associations between all 9 PRS and all 7 symptoms at each of the 6 PRS cutoffs. The following p-value criteria were used to define significance correcting for multiple testing: 7.94×10^{-4} (Bonferroni corrected for 7 symptoms tested on 9 disease PRS, a total of 63 tests), 1.32×10^{-4} (Bonferroni corrected for 63 tests x 6 PRS cutoffs)

We also defined 27 PRS-symptom comparisons as primary hypotheses of interest, chosen to reflect prior associations in the general population between the phenotypes and the diseases from which the PRS were derived. These were:

- Major depressive disorder (MDD) with depression, irritability and apathy
- Bipolar disorder (BPD) with depression and irritability
- Schizophrenia (SCZ) with depression, irritability, psychosis, apathy and violent/aggressive behaviour
- ADHD with irritability, violent & aggressive behaviour and cognitive impairment
- ASD with irritability, psychosis and perseverative/obsessive behaviour
- OCD with perseverative/obsessive behaviour
- Alzheimer's Disease (AD) with depression, irritability, apathy, violent/aggressive behaviour and cognitive impairment
- Parkinson's Disease (PD) with depression, irritability, apathy and cognitive impairment
- Intelligence with cognitive impairment

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Results

The frequency of each symptom in the 5854 HD participants with at least one endorsed symptom (positive or negative) varied from 10.8% (psychosis) to 66.0% (depression), and differed significantly by sex for depression, which was more common in women, and irritability and violent/aggressive behaviour which were both more common in men (**Table 1**). Symptoms were significantly (positively) correlated with each other (**Supplementary Table 2**), resulting in individuals exhibiting multiple symptoms. Of the 5854 HD individuals, 538 had no symptoms, 799 had one symptom, 993 had two symptoms, 1095 had three symptoms, 976 had four symptoms, 795 had five symptoms, 486 had six symptoms and 172 had seven symptoms.

We approximated disease duration as the age at the most recent observation available minus age at motor onset for REGISTRY and Enroll-HD individuals. Mean duration of HD was significantly lower in Enroll-HD, at 6.54 years, than REGISTRY, at 8.14 years ($p=6.55x10^{-21}$). The longer the duration of HD the more likely an individual has experienced a symptom, irrespective of their genetic liability, thus the frequency of any symptom is likely to depend on disease duration.

The effects of CAG length, age at motor onset, sex and disease duration on symptom presence, were tested simultaneously via logistic regression (**Supplementary Table 3**), along with potential differences in symptom frequency between REGISTRY vs Enroll-HD. Increased disease duration was significantly correlated with symptom presence for all symptoms except depression. These associations remained significant when age at most recent visit was included in the model (to account for increasing frequency of symptoms with increasing age) instead of age at motor onset (results not shown). Thus, the increased frequency of symptoms with disease duration cannot simply be attributed to age. Perseverative/obsessive behaviour was seen substantially more frequently in Enroll-HD than REGISTRY participants ($p = 5.72x10^{-10}$), otherwise there were no significant differences.

Table 2 lists the PRS-symptom associations reaching nominal ($p<0.05$) significance, with only the PRS cutoff giving the most significant result being shown. Full PRS-symptom analyses are shown in **Supplementary Tables 4- 12.** The schizophrenia PRS showed significant associations with psychosis, irritability and violent and aggressive behaviour after correction for both the number of PRS-symptom tests and the six PRS cutoffs. The associations of schizophrenia PRS with depression and perseverative/obsessive behaviour were significant after correction for the number of PRS-symptom tests, as was the association between bipolar disorder PRS and depression. Of the primary hypotheses, the following nominally significant associations were also observed: MDD PRS with depression and irritability, ADHD PRS with violent and aggressive behaviour, Parkinson's PRS with cognitive impairment and (interestingly, given the relatively small training GWAS) OCD PRS with perseverative/obsessive behaviour. In each case, increased PRS was associated with an increased risk of the symptom (as shown by odds ratios >1 in **Table 2**). Associations of the intelligence PRS with violent and aggressive behaviour, apathy and cognitive impairment were significant after correction for both the number of PRS-symptom tests and the 6 PRS cutoffs, while the association between intelligence PRS and irritability was significant after correction for the number of PRS-symptom tests. The associations with intelligence PRS have OR <1 in Table 2, indicating that decreased PRS (*i.e.* reduced intelligence) is associated with increased risk of the symptom. Note that the association of

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SCZ PRS with psychosis, irritability, depression and violent and aggressive behaviour remained significant across all p-value cutoffs used to define the PRS (**Figure 1, Supplementary Table 4**), as was the association between intelligence PRS and cognitive impairment (**Figure 2, Supplementary Table 12**), thus increasing confidence that these results are robust. In general, PRS-symptom associations in **Table 2** surviving correction for multiple testing of symptom-PRS comparisons showed at least nominally significant association over a range of PRS cutoffs **(Figures 1 and 2**). Conversely, the association between PD PRS and cognitive impairment was only significant for PRS cutoff p<0.0001 (**Supplementary Table 11**), making it likely that this is a false positive. It can be seen from **Table 2** that the proportion of symptom variance accounted for by the PRS, as measured by the Nagelkerke R^2, is small (<1%). Likewise, the ability of the PRS to distinguish individuals with the symptom from those without, as measured by the AUC, is limited (AUCs <0.55). For comparison, the Psychiatric Genomics Consortium (10) observed that schizophrenia PRS accounted for ~7% of variance in schizophrenia liability, with AUC around 0.7. AUC of 0.8 is generally required for a clinically useful predictor (29).

Since sex, CAG length, age at motor onset and disease duration were found to correlate significantly with symptom risk (**Supplementary Table 3**), the association analyses between PRS and symptom were repeated conditioning on the effects of the factors found to be significantly associated with symptom presence. This made little difference to the significance of the PRS-symptom associations (results not shown). Together, these factors give AUC of 0.57-0.64 (**Supplementary Table 3**), and adding the PRS makes little difference to this (results not shown).

For symptoms with a significant sex association (depression, irritability and violent and aggressive behaviour) and PRS with a significant association in the whole sample, the PRS-symptom association analyses were run in males and females separately (**Supplementary Table 13**). Only the association of MDD PRS (p-value cutoff 0.001) with depression showed nominally significant difference in OR between males and females (male OR=1.01, female OR=1.15, p=0.0386).

Since psychiatric disorders are known to have genetic overlap(9), it follows that the PRS for different disorders are likely to be correlated. Thus, when multiple PRS from different disorders associate with the same symptom, it is unclear which are driving the association. To assess this, we performed logistic regression of each symptom simultaneously on all PRS that were significantly associated after correction for the number of symptom-PRS comparisons (**Table 2**). Symptom-PRS comparisons reflecting primary hypotheses of interest were also included in these analyses if they reached nominal significance (**Table 2**). Depression, irritability, violent and aggressive behaviour and perseverative/obsessive behaviour each had multiple PRS meeting these criteria, and the results for these symptoms are shown in **Supplementary Table 14**. There appears to be a complex relationship between PRS and symptom. For example, MDD, SCZ, BPD and intelligence PRS contribute independently to the risk of depression, and SCZ, intelligence and ADHD PRS to the risk of violent and aggressive behaviour. Notably, only SCZ PRS contributes to psychosis risk, and OCD PRS contributes to the risk of perseverative/obsessive behaviour even after correcting for SCZ PRS.

Several PRS are associated with multiple phenotypes in **Table 2**. Notably, SCZ PRS is associated with depression, irritability, psychosis, violent and aggressive behaviour and perseverative/obsessive behaviour, and BPD PRS with violent and aggressive behaviour, apathy, perseverative/obsessive behaviour and depression. Since the symptoms are correlated, it is unclear which symptom is driving the association. We therefore tested the association between each symptom and PRS conditioning

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on the other symptoms. Results for SCZ PRS are shown in **Supplementary Table 15**, with those for BPD PRS in **Supplementary Table 16**, and those for intelligence PRS in **Supplementary Table 17**. The relationship between PRS and phenotypes is complicated, and differs with the p-value cutoff used to define the PRS. However, it seems that the association between SCZ PRS and psychosis is consistent across PRS cutoffs, and that the associations between SCZ PRS and violent/aggressive and perseverative/obsessive behaviour are largely driven by correlations with other phenotypes. The pattern of symptom associations with intelligence PRS are mainly driven by cognitive impairment, although violent and aggressive behaviour is also associated.

The number of symptoms seen in any individual can be regarded as a surrogate for disease severity, and one might expect this to correlate with PRS. To test this hypothesis, linear regression of PRS on symptom count (0-7) was performed, with the latter treated both as an 8-level factor and a quantitative variable (**Supplementary Table 18**). Quantitative symptom count was found to give more significant associations, suggesting that increased PRS is indeed correlated with increased symptom count. This was particularly marked for SCZ PRS ($p=4.45x10^{-9}$ using a $p<0.05$ cutoff to define PRS, with $p=9.12x10^{-11}$ if apathy and cognition omitted). A similar pattern was observed for the intelligence PRS, with PRS decreasing as number of symptoms increased ($p=5.78x10^{-8}$ using a $p<1$ cutoff to define PRS). Associations between PRS and number of symptoms were also observed for MDD (p=0.0015) and BD (p=0.00268), with the latter being attributable to correlation with SCZ PRS. No other psychiatric PRS showed significant association with symptom count after correction for multiple PRS cutoffs. To test whether association of SCZ PRS with individual symptoms can be explained by the general association with symptom count, the number of other symptoms was included as a covariate in the regression of PRS on symptom presence (**Supplementary Table 19**). Psychosis and irritability were found to be associated with SCZ PRS independently of other symptoms. For the intelligence PRS (**Supplementary Table 20**), cognitive impairment is consistently associated independently of other symptoms, with violent/aggressive behaviour also associated at certain PRS cutoffs.

Discussion

We show a significant genetic overlap between some psychiatric disorders and neuropsychiatric symptoms in HD but little overlap between the two neurodegenerative disorders and neuropsychiatric symptoms or cognition in HD. Cognitive symptoms in HD have a genetic overlap with intelligence (see **Figure 3** for a graphical overview of the pattern of associations). These interpretations are consistent with the observations in the Brainstorm study that found shared genetic risk amongst psychiatric disorders but no overlap between the individual neurological disorders and no overlap with neuropsychiatric symptom risk in neurodegenerative disorders (9). All of the neurological diseases are associated with higher rates of psychiatric symptoms than seen in the populations from which they derive but it seems the psychotic symptoms seen in these disorders have different aetiologies (9). There appears to be no clear association of psychiatric polygenic risk scores with psychiatric symptoms in AD (21) or PD (28). By contrast, in severe monogenic neurodevelopmental disorders, behavioural phenotypes (such as autistic behaviour and developmental delay) have been shown to be modulated by common genetic variation in the same direction as in the population for the traits examined, with similar effect sizes (R^2 of 0.6-0.8%) to those observed here (31). These results, in conjunction with ours, indicate that even in diseases previously assumed to be entirely attributable to single genetic variants, there is a contribution of polygenic risk in influencing phenotypic presentation (30).

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Schizophrenia and bipolar disorder PRS are significantly associated with the presence of multiple psychiatric symptoms in HD. Schizophrenia PRS is associated with psychosis (and irritability) independently of other symptoms and is the only PRS to predict HD psychosis. While psychosis in HD is around ten times more common than in the general population, it is seen in only a minority of cases (2), as in the participants studied here (11%). There are also reports of clustering of psychotic symptoms in HD families (6,7), implying a genetic contribution to these symptoms. Whilst the relationship between the PRS and neuropsychiatric symptoms is complicated, the association between SCZ PRS and psychosis in HD is consistent across PRS thresholds. The other schizophrenia PRS relationships with violent/aggressive and perseverative/obsessive behaviour in HD are largely driven by correlations with other phenotypes. Previously, Tsuang *et al.* (8) tested for association of psychosis in HD with a set of 214 SNPs chosen from candidate genes for schizophrenia, HD or psychosis in neurodegenerative disorders. None of their associations survived correction for multiple testing, possibly due to the small sample size (47 HD cases with psychosis, 126 without psychosis). Of the SNPs tested by Tsuang *et al.*, 183 were available in our data; a polygenic risk score generated from these (with effect sizes taken from the PGC schizophrenia GWAS) showed no association with psychosis in our HD sample (OR=0.97, p=0.536). The highly significant association between schizophrenia PRS and psychosis observed in our sample shows the benefits of a large sample size of HD patients, along with a larger set of SNPs systematically selected for association with schizophrenia in a powerful schizophrenia GWAS. The schizophrenia PRS is also amongst the strongest influences on perseveration, one of the most characteristic behavioural problems in HD. The PRS for OCD also influences the presence of perseverative/obsessive behaviour, despite the OCD PRS having been derived from a much smaller and less powerful sample than that for schizophrenia.

Schizophrenia may be regarded as a neurodevelopmental disorder with origins in foetal development that manifest in symptoms most usually in early adulthood (31), whereas psychotic symptoms in HD generally manifest later in life (2,32). The genes that contribute to the schizophrenia PRS are preferentially expressed in the medium spiny neurons of the striatum (33), which are the most vulnerable cell types in HD: by the time HD motor symptoms are manifest up to half of these neurons have died (34). Susceptibility to psychiatric symptoms in surviving cells is influenced by the schizophrenia polygenic risk, and provides a potential explanation for the increased rates of psychotic symptoms observed in HD patients.

Cognitive decline and dementia are an inevitable part of HD progression, with executive and psychomotor function often the first deficits noted, with memory problems later in disease (2). Longer CAG repeat tracts are associated with increased risk of cognitive deficits in our sample: the previous data on this relationship have been inconsistent (2,35). Recent studies have shown that poorer performance in the symbol digit modality test was associated with longer *HTT* CAG repeat lengths (36), and poorer cognitive function was seen with increasing repeat lengths in the disease causing range (37). The clinical characteristics questionnaire used to assess symptoms for this study seeks an integrated measure of cognitive decline by asking about problems that might interfere with performing everyday functions and is relatively crude, though this will be partly offset by the larger size of our study (1000s rather than the 100s of participants).

It is notable that neither apathy nor cognitive dysfunction in HD are correlated with PRS for psychiatric or neurodegenerative disorders apart from nominal associations between apathy and schizophrenia and bipolar PRS, which become non-significant when accounting for the presence of

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other symptoms (see **Supplementary Tables 15 and 16**). However, both are significantly correlated with a PRS measuring intelligence. This suggests that both neuropsychiatric and cognitive symptoms in HD patients exhibit shared genetics with related disorders in the general population., and is also consistent with apathy being the only psychiatric symptom to correlate with disease progression (38) Higher PRS for intelligence is associated with later cognitive decline in HD, as it is in AD (14). The genes associated with intelligence are highly expressed in medium spiny neurons of the striatum and pyramidal neurons of the CA1 hippocampus (14), early targets of degeneration in HD and AD respectively, potentially contributing to the severe cognitive decline seen in these diseases. Surprisingly, there is no significant association between the presence of cognitive deficits in HD and genetic risk for AD, though AD PRS predicts memory decline and poorer cognitive performance in healthy children and adults well before the age of risk for AD (39,40). In children, *HTT* CAG repeat length itself shows a J-shaped relationship with cognition, with maximum cognition at 40-41 repeats (37). Since higher intelligence is associated with better health and increased well-being (41), there may thus be a selective advantage of longer *HTT* CAG repeat length, below the threshold for HD, in the wider population.

Depression is very common in HD and more common in females (2). There is a significant correlation in our sample of increased likelihood of depression with shorter CAG repeat lengths in the disease causing allele in *HTT* (**Supplementary Table 3**), along with an association with earlier age at motor onset. The reason for these associations is unclear; the obvious explanation that longer disease duration makes depression more likely is not true in our sample (Supplementary Table 3). In fact, the apparent associations between depression and both age at motor onset and CAG repeat length are explained by the residual of age at motor onset after correction for CAG length (see (5) for how this is derived). Participants with an earlier than expected age at onset (given their CAG length) are more likely to have depression. This could be due to increased environmental stress among individuals with earlier motor onset, and also that some genetic modifiers of age at motor onset may also be associated with depression in HD. The few previous studies, each examining less than 100 participants, detected no relationship between CAG length and presence of depression (42–44). In the non-disease causing range, longer *HTT* CAG length from 24 to 38 repeats was associated with an increased likelihood of depression (45). The PRS for major depressive disorder, bipolar disorder and schizophrenia are all independently associated with the presence of depression in HD, which is consistent with their known shared heritability (9).

Irritability, like depression, is very common in HD and has a significantly reduced likelihood with longer CAG length (**Supplementary Table 3**) but unlike depression, longer duration of disease makes irritability more likely. This association is not explained by increased age. Violent/aggressive behaviour can be considered to be an extreme manifestation of irritability, and the most significant shared heritability with the highest odds ratio for both is the schizophrenia PRS. The ADHD and bipolar disorder PRS also contribute independently to the presence of violent/aggressive behaviour. As in the wider population violence and aggressive behaviour is more common in men (2).

The study presented here has a number of limitations. As noted, the clinical characteristics questionnaire is a relatively crude instrument. We found that disease duration (defined as the age at the most recent observation available minus age at motor onset) greatly influences the likelihood of developing any symptom. The Enroll-HD sample participants have significantly lower disease duration than those in REGISTRY: after correction, symptom frequencies were generally similar in

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both samples. Correcting for duration (and other factors influencing symptom risk such as sex) does not materially change the PRS associations. The larger size of this study compared with previous studies partly mitigates its limitations, and these initial findings provide a platform for more detailed studies using specific psychiatric instruments. All Enroll-HD participants now undergo a short problem behaviours assessment battery (PBA), which may account for the increased frequency of perseverative/obsessive behaviour observed in Enroll-HD relative to REGISTRY. An examination of the association of the psychiatric PRS with the age at onset of symptoms, in light of the much later onset of psychosis in HD than is usual in schizophrenia or bipolar disorder, could shed further light on these vulnerabilities. It would be useful to investigate further the predictive power of the PRS using more detailed clinical data on the psychiatric symptoms in HD which might help in disease management. It would also be interesting to explore the overlap of multiple symptoms and the psychiatric and cognitive PRS to attempt to establish directions of causation.

It is notable that the PRS for psychiatric diseases associate with increased risk of developing parallel phenotypic behavioural and psychiatric symptoms in HD participants. The data available in the ongoing Enroll-HD study will provide for a much more detailed analyses of these symptoms, their aetiology and treatment and may in turn inform the psychiatric diseases. The lack of genetic overlap with other neurodegenerative disorders, consistent with the Brainstorm study (9), implies different underlying pathways leading to degeneration in the different neurodegenerations that may relate to the disease-specific characteristic differential neuronal vulnerabilities to degeneration. Striatial medium spiny neurons are most vulnerable in HD, dopaminergic neurons of the substantia nigra in PD and hippocampal and entorhinal cortical neurons in AD. The differential vulnerability may relate to pathways essential to the survival and continued function of each specific cell type and these are likely to be different in different neurodegenerations (46). Thus, psychiatric symptoms may be mediated by common dysfunctional pathways in surviving cells whereas cognitive and neurodegenerative symptoms are likely due to specific regional cellular populations degenerating via different pathways.

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Conflicts of interest

J.F.G and V.C.W have a financial interest in Triplet Therapeutics, Inc., a company developing new therapeutic approaches to address triplet repeat disorders such Huntington's Disease and Myotonic Dystrophy. J.F.G and V.C.W's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

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J.D.L is a paid advisory board member for F. Hoffman-La Roche Ltd, Wave Life Sciences USA Inc, Huntington Study Group (for uniQuire biopharma B.V.), and Mitoconix Bio Limited. J.D.L is also a paid consultant for Vaccinex Inc and Azevan Pharmaceuticals Inc.

D.G.M has been a scientific consultant and/or received an honoraria or stock options from Biogen Idec, AMO Pharma, Charles River, Vertex Pharmaceuticals, Triplet Therapeutics, LoQus23, BridgeBio and Small Molecule RNA, and had a research contract with AMO Pharma.

E.R.D. has provided consulting services to 23andMe, Lundbeck, Abbott, MC10, Roche, Abbvie Pharmaceuticals, MedAvante, Sanofi, American Well, Medical-legal services, Shire, Biogen, Mednick Associates, Sunovion Pharma, Clintrex, Teva Pharmaceuticals, DeciBio, Olson Research Group, Denali Therapeutics, Optio, Voyager Therapeutics, GlaxoSmithKline, Prilenia Advisory Board, Grand Rounds, Putnam Associates, received research support from Abbvie Pharmaceuticals, Acadia Pharmaceuticals, AMC Health, Biosensics, GlaxoSmithKline, Nuredis Pharmaceuticals, Pfizer, Prana Biotechnology, Raptor Pharmaceuticals, Roche and Teva Pharmaceuticals, acted as Editor of *Digital Biomarkers* for Karger Publications and has an ownership interest in Blackfynn (data integration company) and Grand Rounds (second opinion service).

G.B.L. has provided consulting services, advisory board functions, clinical trial services and/or lectures for Allergan, Alnylam, Amarin, AOP Orphan Pharmaceuticals AG, Bayer Pharma AG, CHDI Foundation, GlaxoSmithKline, Hoffmann-LaRoche, Ipsen, ISIS Pharma, Lundbeck, Neurosearch Inc, Medesis, Medivation, Medtronic, NeuraMetrix, Novartis, Pfizer, Prana Biotechnology, Sangamo/Shire, Siena Biotech, Temmler Pharma GmbH and Teva Pharmaceuticals. He has received research grant support from the CHDI Foundation, the Bundesministerium für Bildung und Forschung (BMBF), the Deutsche Forschungsgemeinschaft (DFG), the European Commission (EU-FP7, JPND). His study site Ulm has received compensation in the context of the observational Enroll-HD Study, TEVA, ISIS and Hoffmann-Roche and the Gossweiler Foundation. He receives royalties from the Oxford University Press and is employed by the State of Baden-Württemberg at the University of Ulm.

E.v.D. has provided consulting services to Azevan Pharmaceuticals and Teva Pharmaceutical Industries Ltd., and advisory board service for Lundbeck.

J.S.P. has provided consulting services and advisory board functions for Wave Life Sciences, Lundbeck, and Roche.

H.R. has performed consultancy work for Roche.

D.J.McL is currently employed as a clinical fellow in clinical trials funded in part by CHDI, UCB Pharma and Roche. He holds a Welsh Assembly Government funded WCAT fellowship and has received grant funding from the MRC and Cardiff University.

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Tables

Table 1: Symptom counts and sex differences in the 5854 individuals with at least one recorded symptom diagnosis (positive or negative).

Symptom	Freq (%)	Male		Female		OR(F/M)	P(F/M)
		Y	N	Y	N		
Depression	66.0	1639	1120	2116	816	1.75 (1.57,1.96)	<2e-16
Irritability	60.3	1757	1005	1675	1252	0.77 (0.69,0.85)	8.76e-7
Psychosis	10.8	299	2396	301	2562	0.94 (0.79,1.12)	0.485
VAB	31.2	965	1794	802	2107	0.71 (0.63,0.79)	1.90e-9
Apathy	53.8	1484	1291	1581	1344	1.02 (0.92,1.14)	0.664
POB	37.5	1048	1713	1076	1833	0.96 (0.86,1.07)	0.451
Cognitive impairment	57.5	1583	1214	1726	1235	1.07 (0.97,1.19)	0.194

VAB= violent/aggressive behaviour, POB=perserverative/obsessive behaviour. Freq(%) is the frequency of the symptom among individuals in the sample for whom a diagnosis of that symptom was recorded.

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Table 2 HD symptom-PRS associations reaching nominal significance

SYMPTOM	PRS	PRS CUT-OFF	OR	R^2 (%)	AUC	P VALUE
Depression	*Schizophrenia*	*0.05*	*1.12*	*0.37*	*0.528*	*2.47×10^{-4}*
	BPD	*0.01*	*1.11*	*0.36*	*0.532*	*3.06×10^{-4}*
	Intelligence	0.001	0.93	0.18	0.519	9.51×10^{-3}
	MDD	0.001	1.08	0.17	0.523	0.0129
Irritability	**Schizophrenia**	**0.05**	**1.17**	**0.76**	**0.542**	**1.03×10^{-7}**
	Intelligence	*1*	*0.90*	*0.37*	*0.531*	*1.99×10^{-4}*
	MDD	1	1.06	0.11	0.518	0.0444
Psychosis	**Schizophrenia**	**0.001**	**1.20**	**0.64**	**0.548**	**5.98×10^{-5}**
	Alzheimer's	0.001	1.10	0.19	0.529	0.0265
	Intelligence	0.0001	0.90	0.24	0.534	0.0147
VAB	**Intelligence**	**0.01**	**0.89**	**0.50**	**0.537**	**2.44×10^{-5}**
	Schizophrenia	**0.05**	**1.13**	**0.46**	**0.532**	**5.46×10^{-5}**
	BPD	*0.001*	*1.11*	*0.34*	*0.527*	*5.35×10^{-4}*
	ADHD	0.05	1.09	0.22	0.523	5.26×10^{-3}
	MDD	0.001	1.08	0.17	0.521	0.0136
	ASD	0.01	1.06	0.11	0.517	0.0451
POB	*Schizophrenia*	*0.01*	*1.12*	*0.39*	*0.531*	*1.47×10^{-4}*
	BPD	0.5	1.08	0.18	0.521	9.25×10^{-3}
	Intelligence	0.01	0.93	0.18	0.521	0.0103
	OCD	0.001	1.07	0.15	0.521	0.0190
	MDD	0.001	1.07	0.13	0.521	0.0292
Apathy	**Intelligence**	**1**	**0.90**	**0.41**	**0.534**	**9.27×10^{-5}**
	BPD	0.001	1.07	0.14	0.519	0.0222
	Schizophrenia	0.0001	1.07	0.13	0.518	0.0254
	ASD	0.001	1.06	0.10	0.516	0.0499
Cognitive impairment	**Intelligence**	**0.01**	**0.89**	**0.45**	**0.535**	**3.90×10^{-5}**
	Parkinson's	0.0001	1.09	0.26	0.524	1.67×10^{-3}
	MDD	0.001	1.06	0.11	0.516	0.0403

VAB= violent/aggressive behaviour, POB=perserverative/obsessive behaviour. MDD= major depressive disorder. BPD= bipolar disorder. ASD= autism spectrum disorder. ADHD = attention deficit hyperactivity disorder. R^2= Nagelkerke R^2. OR= Odds ratio for presence of symptom associated with 1 s.d. increase in PRS.

Results in *italics* satisfy the Bonferroni corrected p-value cut-off 7.94×10^{-4} (corrected for 63 possible PRS-phenotype comparisons), and results in **bold** satisfy the Bonferroni corrected p-value cut of 1.32×10^{-4} (corrected for the 63 PRS-symptom comparisons and 6 PRS cut-offs). Primary symptom-PRS hypotheses (see text) are underlined.

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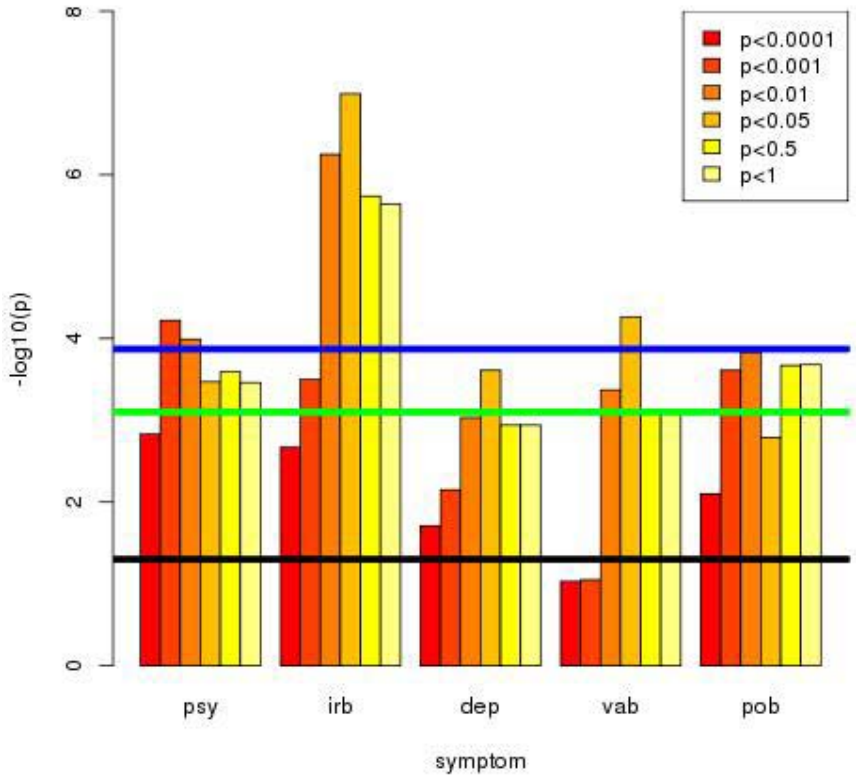

Figure 1. Association between increased schizophrenia PRS and increased symptom frequency. Numbers in the box correspond to the p-value thresholds used to derive the PRS. Black line corresponds to nominally significant association (p=0.05). Green line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons (9 PRS x 7 symptoms). Blue line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons and 6 PRS cutoffs. Note: Only symptoms with at least one p-value reaching the green line are shown.

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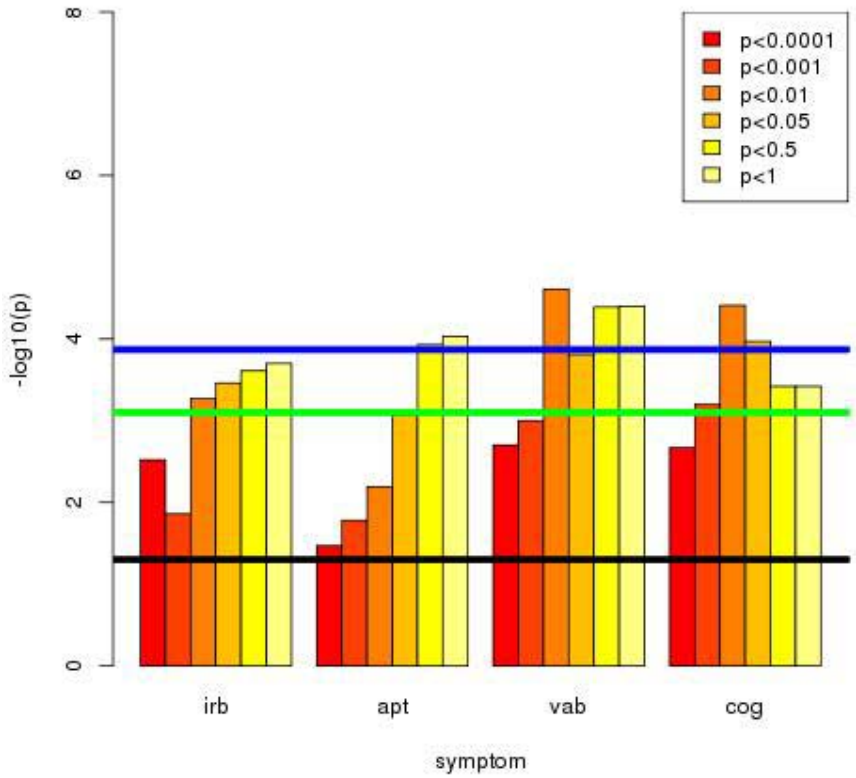

Figure 2. Association between decreased intelligence PRS and increased symptom frequency. Numbers in the box correspond to the p-value thresholds used to derive the PRS. Black line corresponds to nominally significant association (p=0.05). Green line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons (9 PRS x 7 symptoms). Blue line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons and 6 PRS cutoffs. Note: Only symptoms with at least one p-value reaching the green line are shown

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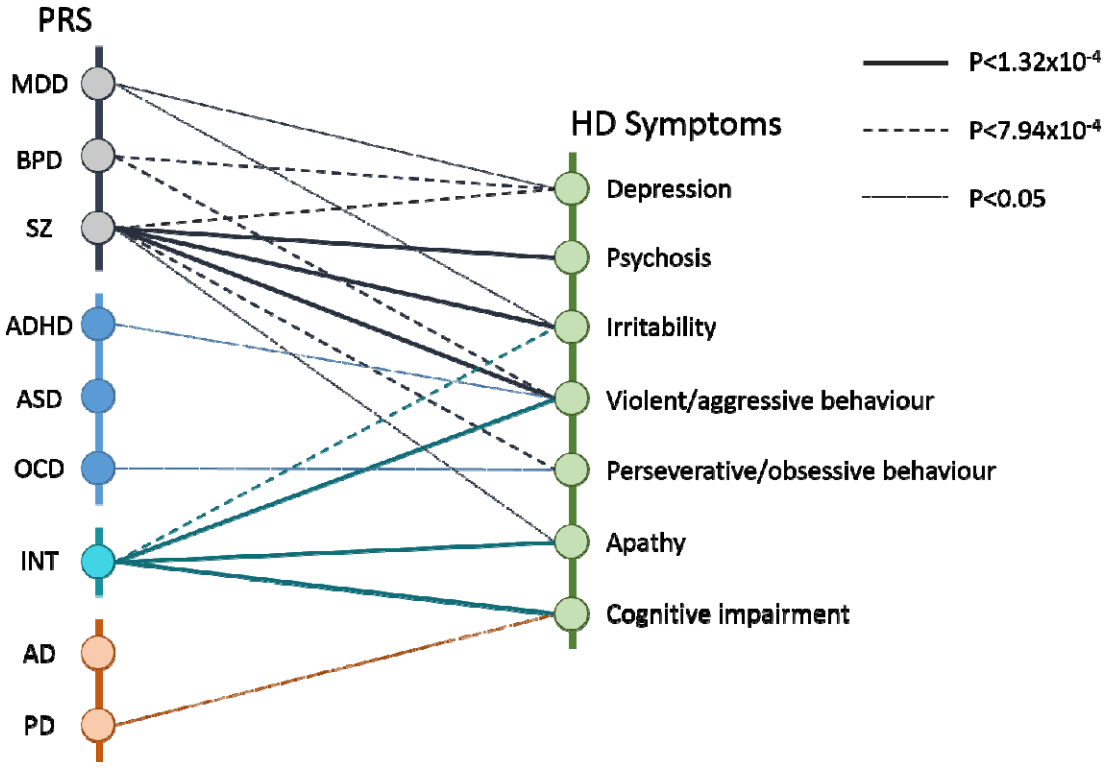

Figure 3. Pattern of association between HD neuropsychiatric and cognitive phenotypes and psychiatric/neurodegenerative/cognitive disorders. Pattern of association between non-motor phenotypes in HD and PRS from psychiatric (black), neurodevelopmental (blue), neurodegenerative (orange) and cognitive (cyan) disorders. Solid lines show associations significant after correcting for 63 PRS-symptom combinations (9 PRS x 7 symptoms) and 6 PRS cutoffs ($p<1.32x10^{-4}$). Dashed lines show associations significant after correcting for 63 PRS-symptom combinations ($p<7.94x10^{-4}$). Dotted lines show nominally-significant associations ($p<0.05$) in PRS-symptom combinations that were part of the primary analysis.