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# Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

The International Schizophrenia Consortium\*

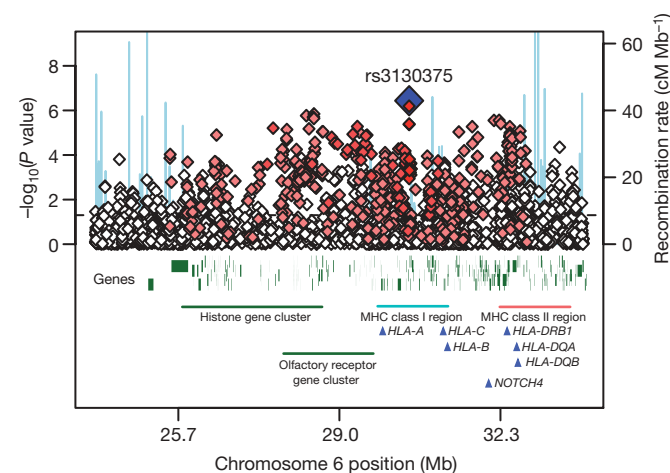
Schizophrenia is a severe mental disorder with a lifetime risk of about 1%, characterized by hallucinations, delusions and cognitive deficits, with heritability estimated at up to 80%<sup>1,2</sup>. We performed a genome-wide association study of 3,322 European individuals with schizophrenia and 3,587 controls. Here we show, using two analytic approaches, the extent to which common genetic variation underlies the risk of schizophrenia. First, we implicate the major histocompatibility complex. Second, we provide molecular genetic evidence for a substantial polygenic component to the risk of schizophrenia involving thousands of common alleles of very small effect. We show that this component also contributes to the risk of bipolar disorder, but not to several non-psychiatric diseases.

We genotyped the International Schizophrenia Consortium (ISC) case-control sample for up to ~1 million single nucleotide polymorphisms (SNPs), augmented by imputed common HapMap SNPs. In the genome-wide association study (GWAS; genomic control  $\lambda_{GC} = 1.09$ ; Supplementary Table 1 and Supplementary Figs 1–3), the most associated genotyped SNP ( $P = 3.4 \times 10^{-7}$ ) was located in the first intron of myosin XVIIIIB (*MYO18B*) on chromosome 22. The second strongest association comprised more than 450 SNPs on chromosome 6p spanning the major histocompatibility complex (MHC; Fig. 1). There is some evidence for between-site heterogeneity in both allele frequencies and odds ratios (Table 1). We observed associations consistent with previous reports in the 22q11.2 deletion region and *ZNF804A* (ref. 3) (Supplementary

Table 2, Supplementary Fig. 2 and section 5 and 6 in Supplementary Information).

The best imputed SNP, which reached genome-wide significance (rs3130297,  $P = 4.79 \times 10^{-8}$ , T allele odds ratio = 0.747, minor allele frequency (MAF) = 0.114, 32.3 megabases (Mb)), was also in the MHC, 7 kilobases (kb) from *NOTCH4*, a gene with previously reported associations with schizophrenia<sup>4</sup>. We imputed classical human leukocyte antigen (HLA) alleles; six were significant at  $P < 10^{-3}$ , found on the ancestral European haplotype<sup>5</sup> (Table 1, Supplementary Table 3 and section 3 in Supplementary Information). However, it was not possible to ascribe the association to a specific HLA allele, haplotype or region (Supplementary Table 3 and Supplementary Fig. 4).

We exchanged GWAS summary results with the Molecular Genetics of Schizophrenia (MGS) and SGENE consortia for genotyped SNPs with  $P < 10^{-3}$ . There were 8,008 cases and 19,077 controls of European descent in the combined sample (see refs 6, 7 and section 7 in Supplementary Information). Our top genotyped MHC SNP (rs3130375) had  $P = 0.086$  and  $P = 0.14$  in MGS and SGENE, respectively. Considering the combined results for genotyped and imputed SNPs across the MHC region more broadly, rs13194053 had a genome-wide significant combined  $P = 9.5 \times 10^{-9}$  (ISC, MGS and SGENE:  $P = 3 \times 10^{-4}$ ,  $1 \times 10^{-2}$  and  $1 \times 10^{-4}$ , respectively; C allele



**Figure 1 | Association results across the MHC region.** Results are shown as  $-\log_{10}(P \text{ value})$  for genotyped SNPs. The most associated SNP is shown as a blue diamond. The colour of the remaining markers reflects  $r^2$  with rs3130375, light pink,  $r^2 > 0.1$ , red,  $r^2 > 0.8$ . The recombination rate from the CEU HapMap (second y axis) is plotted in light blue.

**Table 1 | MHC association for the most significant genotyped SNP rs3130375**

a MHC association for rs3130375 by sample

Sample	Ancestry	Frequency (rs3130375, A allele)		
		Cases	Controls	<i>P</i> value
University of Aberdeen	Scottish	0.132	0.168	0.0060
University of Edinburgh	Scottish	0.137	0.135	0.8930
University College London*	British	0.132	0.143	0.4836
Trinity College Dublin	Irish	0.110	0.170	0.0012
Cardiff University	Bulgarian	0.077	0.084	0.5602
Portuguese Island Collection	Portuguese	0.048	0.061	0.3510
Karolinska Institutet (5.0)	Swedish	0.043	0.119	0.0004
Karolinska Institutet (6.0)	Swedish	0.089	0.142	0.0040

b MHC association for rs3130375 for classical HLA alleles with  $P < 1 \times 10^{-3}$

HLA allele	Frequency†	Odds ratio	<i>P</i> value
<i>HLA-A*0101</i>	0.103	0.785	$4 \times 10^{-5}$
<i>HLA-C*0701</i>	0.113	0.778	$5 \times 10^{-5}$
<i>HLA-B*0801</i>	0.068	0.757	$3 \times 10^{-5}$
<i>HLA-DRB*0301</i>	0.121	0.768	$3 \times 10^{-6}$
<i>HLA-DQB*0201</i>	0.210	0.857	$4 \times 10^{-4}$
<i>HLA-DQA*0501</i>	0.205	0.798	$6 \times 10^{-7}$

Total sample Cochran–Mantel–Haenszel  $P = 4 \times 10^{-7}$ ; Breslow–Day heterogeneity test  $P = 0.012$  (d.f. = 6).

\* SNP failed genotyping quality control in UCL. Allele frequency for UCL based on imputed genotypes.

† Frequency is estimated population frequency.

\*Lists of authors and their affiliations appear at the end of the paper.

odds ratio = 0.82, 0.88 and 0.78) and was in linkage disequilibrium with rs3130375 ( $r^2 = 0.35$  in HapMap). Across the region, 11 other SNPs had  $P < 10^{-7}$  at 27.1–27.3 Mb and 32.7 Mb (Supplementary Table 5).

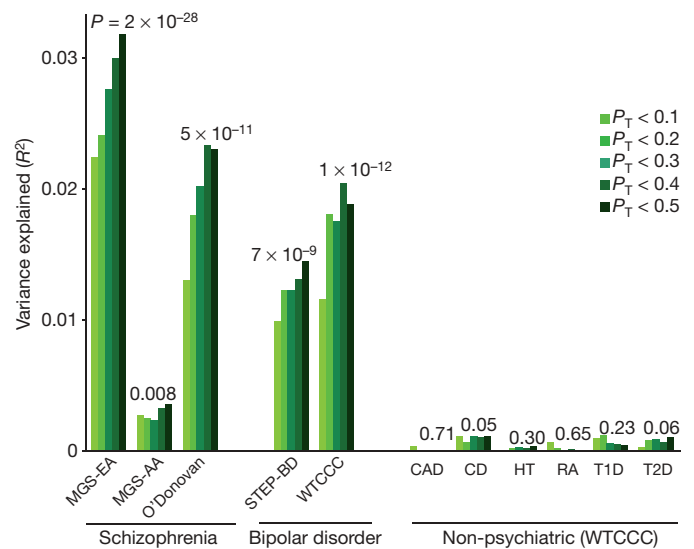
Our second approach was to evaluate whether common variants have an important role en masse, directly testing the classic theory of polygenic inheritance<sup>8</sup>, previously hypothesized to apply to schizophrenia<sup>9</sup>. Although our GWAS analysis did not identify a large number of strongly associated loci, there could still be potentially thousands of very small individual effects that collectively account for a substantial proportion of variation in risk. We summarized variation across nominally associated loci into quantitative scores, and related the scores to disease state in independent samples<sup>10</sup>. Although variants of small effect (for example, genotypic relative risk (GRR) = 1.05) are unlikely to achieve even nominally significant  $P$  values, increasing proportions will be detected at increasingly liberal significance thresholds ( $P_T$ ), for example,  $P_T < 0.1$  or  $P_T < 0.5$ . Using such thresholds, we defined large sets of ‘score alleles’ in a discovery sample, to generate aggregate risk scores for individuals in independent target samples. We use the term score, instead of risk, as we cannot differentiate the minority of true risk alleles from unassociated variants.

We performed the score analyses on a reduced set of SNPs to facilitate analysis and interpretation. After filtering on MAF, genotyping rate and linkage disequilibrium (independent of association with schizophrenia), we obtained a subset of 74,062 autosomal SNPs in approximate linkage equilibrium (Supplementary Tables 6 and 7). In each discovery sample, we selected sets of score alleles at different association test  $P_T$  thresholds. For each individual in the target sample, we calculated the number of score alleles they possessed, each weighted by the log odds ratio from the discovery sample. To assess whether the aggregate scores reflect schizophrenia risk, we tested for a higher mean score in target cases compared to controls (sections 9–11 in Supplementary Information and Supplementary Table 7).

We selected males (2,176 cases, 1,642 controls) and females (1,146 cases, 1,945 controls) to form arbitrary discovery and target samples (Supplementary Table 8). Score alleles designated in the discovery sample were significantly enriched among target cases, and the effect was larger for increasingly liberal  $P_T$  thresholds. The score on the basis of all SNPs with male discovery  $P_T < 0.5$  ( $n = 37,655$  SNPs) was highly correlated with schizophrenia in target females ( $P = 9 \times 10^{-19}$ ), explaining  $\sim 3\%$  of the variance (Nagelkerke’s pseudo  $R^2$  from logistic regression), with higher scores in cases. The results were not driven by only a few highly associated regions (section 12 in Supplementary Information).

We eliminated several possible confounders, with emphasis on subtle population stratification (Supplementary Tables 9–15). Defining score alleles in British Isles samples and testing in target samples from Sweden, Portugal and Bulgaria, and vice versa, we observed a similar pattern of results. It is unlikely that the same substructure is overrepresented in the corresponding phenotype class when discovery and target samples are from distinct populations. The effect is also stronger for SNPs within annotated genes (Supplementary Table 16).

We used independent GWAS samples to replicate the polygenic component, to examine whether this component is shared with bipolar disorder<sup>11</sup>, and to demonstrate specificity by considering non-psychiatric diseases. We used the entire ISC for the discovery sample, considering the five most informative  $P_T$  thresholds from the intra-ISC analyses. The independent target samples were the MGS European-American (MGS-EA), the MGS African-American (MGS-AA) and the UK sample described previously by O’Donovan *et al.*<sup>8</sup>. The ISC-derived score was highly associated with disease in both European schizophrenia samples (Fig. 2, Supplementary Fig. 6 and Supplementary Table 17). The MGS-EA had a significantly higher mean  $P_T < 0.5$  score in cases compared to controls ( $P = 2 \times 10^{-28}$ ,  $R^2 = 3.2\%$ ), as did the smaller O’Donovan sample ( $P = 5 \times 10^{-11}$ ,



**Figure 2 | Replication of the ISC-derived polygenic component in independent schizophrenia and bipolar disorder samples.** Variance explained in the target samples on the basis of scores derived in the entire ISC for five significance thresholds ( $P_T < 0.1, 0.2, 0.3, 0.4$  and  $0.5$ , plotted left to right in each study). The y axis indicates Nagelkerke’s pseudo  $R^2$ ; the number above each set of bars is the  $P$  value for the  $P_T < 0.5$  target sample analysis. CAD, coronary artery disease; CD, Crohn’s disease; HT, hypertension; RA, rheumatoid arthritis; T1D, type I diabetes; T2D, type II diabetes. Numbers for cases/controls: MGS-EA 2,687/2,656; MGS-AA 1,287/973; O’Donovan 479/2,938; STEP-BD 955/1,498; WTCCC 1,829/2,935; CAD 1,926/2,935; CD 1,748/2,935; HT 1,952/2,935; RA 1,860/2,935; T1D 1,963/2,935; and T2D 1,924/2,935.

$R^2 = 2.3\%$ ). Aggregate differences in allele frequencies and patterns of linkage disequilibrium between Europeans and African-Americans are expected to lead to an attenuated effect. Still, MGS-AA cases carried more of the European-derived score alleles than the MGS-AA controls ( $P = 0.008$ ;  $R^2 = 0.4\%$ ).

The ISC-derived score alleles were also associated with bipolar disorder in two independent samples. Both samples, STEP-BD<sup>12</sup> and WTCCC<sup>13</sup>, had higher mean  $P_T < 0.5$  scores in cases than in controls ( $P = 7 \times 10^{-9}$ ,  $R^2 = 1.9\%$ , and  $P = 1 \times 10^{-12}$ ,  $R^2 = 1.4\%$ , respectively) indicating a substantial, shared genetic component.

To test disease specificity, we selected all six non-psychiatric WTCCC samples (coronary artery disease, Crohn’s disease, hypertension, rheumatoid arthritis, type I and type II diabetes). Controls are shared among the WTCCC case samples, including bipolar disorder. In contrast to schizophrenia and bipolar disorder, there was no association ( $P > 0.05$ ) between the ISC-derived schizophrenia scores and these non-psychiatric diseases, for any  $P_T$  threshold.

We next investigated the genetic models consistent with our data. The total additive genetic variance ( $V_A$ ) reflects the number of causal alleles, as well as their frequency and effect size distributions. However, the variance explained by the markers that tag these causal alleles ( $V_M$ ) will be attenuated, reflecting the average extent of linkage disequilibrium between marker and causal allele. In our target samples, the variance explained by the observed score alleles ( $V_S$ ) will be further attenuated by sampling variation and  $P_T$  threshold, such that  $V_S \leq V_M \leq V_A$ .

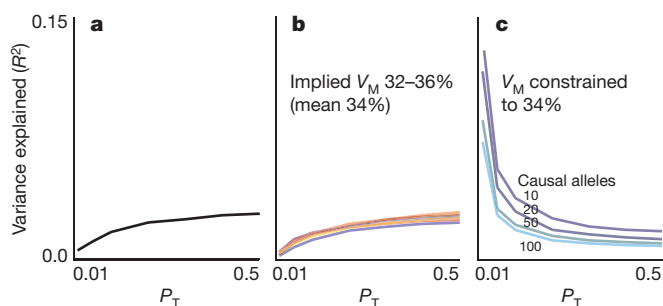
We used simulation to estimate possible values for  $V_M$  and  $V_A$ , by identifying models that produced profiles of  $V_S$  across  $P_T$  threshold that were similar to those observed in the ISC data, as indexed by the target sample  $R^2$ . Under a variety of genetic models, we simulated discovery and target data sets of comparable sample size to the ISC. On the basis of the empirical allele frequency distribution, we simulated marker SNPs, varying the proportion that were in linkage disequilibrium with causal variants, for which we varied allele frequency (uniform, U-shaped) and effect size distributions (fixed

GRR values, exponential GRR values, or fixed variance explained) as well as the extent of linkage disequilibrium (section 16 in Supplementary Information).

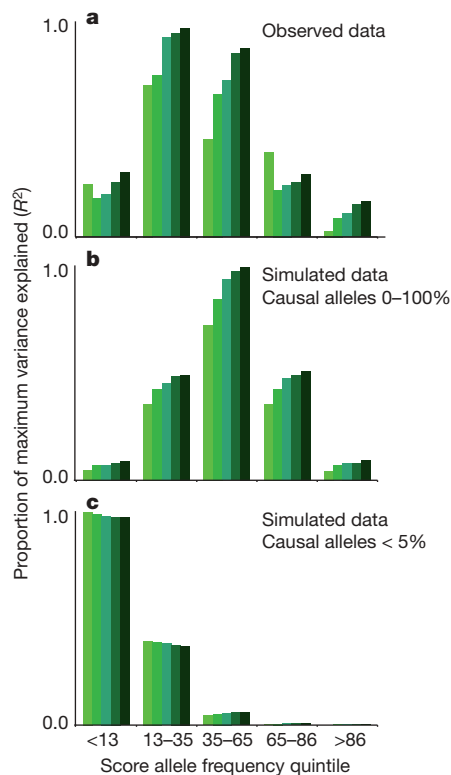
From a broad range of models, a subset produced results consistent with the ISC data (Fig. 3 and Supplementary Fig. 7). Among these, all led to similar estimates of  $V_M$  (mean 34%, range 32% to 36%). In models in which the causal alleles were imperfectly tagged ( $r^2 < 1$ ), estimates of  $V_A$  can be considerably larger. Therefore, our estimate that common polygenic variation accounts for one-third of the total variation in schizophrenia risk is a lower bound for the true value, which could be much higher. Figure 3b shows seven examples from the range of consistent models, detailed in Supplementary Table 18.

The simulated models consistent with our observed results all indicated a substantial number of common variants, whereas models that invoked only a few common variants of large effect or only rare variants were not able to account for our findings. For example, if  $V_M \approx 34\%$  arose from only 100 common causal alleles, with GRR values at the tagging marker between  $\sim 1.2$ – $1.5$ , most would be detected at  $P_T < 0.01$ , and so the variance explained would decline, not increase, as more SNPs were added (Fig. 3c and Supplementary Table 19). It is possible that an observed GRR of  $\sim 1.05$  could represent a large effect of a weakly tagged rare variant, for example, a tenfold effect of a 1/10,000 variant in complete linkage disequilibrium ( $D' = 1$ , but low  $r^2$ ) with a genotyped SNP. However, as this would only hold for low frequency markers (MAF  $< \sim 0.1$ ), we stratified our analysis by score allele frequency (Fig. 4a). For simulated models in which all causal variants were of low frequency ( $< 0.05$ ), a stratified analysis revealed the expected, skewed distribution (Fig. 4c and section 17 in Supplementary Information), which was more pronounced for rarer causal alleles, for example, 1/1,000 (data not shown). In contrast, models in which causal alleles followed a uniform frequency distribution provided a closer fit to our data (Fig. 4b; although note some enrichment in the second quintile, of  $\sim 13$ – $35\%$  score alleles). Moreover, rare variants are likely to be population specific and if recurrent, in linkage disequilibrium with different common alleles within and between populations. As such, they could not account for the observation of disease variation that is largely shared across our different populations.

Decreased reproductive fitness in schizophrenia<sup>14</sup> suggests that risk alleles of large to moderate effect will be under negative selection and therefore very rare<sup>15,16</sup>. This is not inconsistent with our results, because



**Figure 3 | Observed and simulated profiles of target sample variance explained.** **a**, The observed variance explained is shown ( $R^2$ , black line). **b**, A subset of models that produced results consistent with the observed data is shown. All yielded similar estimates of the total variance explained by the SNPs that tag the causal variants,  $V_M$ , with a mean value of 34%. The seven models (shown as percentage SNPs, mean GRR/variance explained ( $V$ ) per causal allele, linkage disequilibrium, and frequency model) were:  $M_1$ : 6.25%, GRR = 1.05,  $r^2 = 1$ , empirical;  $M_2$ : 25%, GRR = 1.025,  $r^2 = 1$ , empirical;  $M_3$ : 12%, GRR = 1.05,  $r^2 < 1$ , uniform;  $M_4$ : 32%, GRR = 1.04,  $r^2 < 1$ , U-shaped;  $M_5$ : 11%,  $V = 0.00006$ ,  $r^2 = 1$ , empirical;  $M_6$ : 25%, GRR(exponential) = 1.025,  $r^2 < 1$ , uniform;  $M_7$ : 100%, GRR(exponential) = 1.012,  $r^2 < 1$ , uniform. **c**, Four inconsistent models with fewer variants of larger effect are shown.



**Figure 4 | Analysis stratified by score allele frequency.** **a**, The observed data for the ISC/MGS-EA comparison is shown. The y-axis is the target sample pseudo  $R^2$ , scaled within each figure as a proportion of the maximum value observed for five significance thresholds ( $P_T < 0.1, 0.2, 0.3, 0.4$  and  $0.5$ , plotted left to right in each quintile). **b**, **c**, Shown are results for simulated data: the common variant model, with a uniform frequency distribution for causal risk-increasing alleles (**b**) and a multiple rare variant model, in which the collective frequency of rare variants at a locus that all reside on the same haplotypic background with respect to the genotyped SNP was bounded at a maximum of 5% (**c**).

the common variants indexed by our polygenic score will not be subjected to strong selection, by virtue of their very small individual effect sizes. Our results do not exclude important contributions of rare variants for schizophrenia<sup>15</sup>, because rare variants are expected as part of the allele frequency/effect size spectrum of a polygenic model. We and others recently reported higher genome-wide rates of rare copy number variants in schizophrenia<sup>17–19</sup>. However, our results indicate that medical sequencing and studies of structural variation to identify rare, highly penetrant variants will not alone fully characterize the genetic risk factors.

In conclusion, our molecular genetic data strongly support a polygenic basis to schizophrenia that (1) involves common SNPs, (2) explains at least one-third of the total variation in liability, (3) is substantially shared with bipolar disorder, and (4) is largely not shared with several non-psychiatric diseases. We also identified variants in the MHC region that received support in two independent studies, although the population specificity and extensive linkage disequilibrium will make follow-up challenging.

A highly polygenic model suggests that genetically influenced individual differences across domains of brain development and function may form a diathesis for major psychiatric illness, perhaps as multiple growth and metabolic pathways influence human height<sup>20</sup>. Our results may also reflect heterogeneity, such that some patients have aetiologically distinct diseases. The shared genetic liability between schizophrenia and bipolar disorder, previously suggested by clinical and genetic epidemiology<sup>11,21</sup>, opens up the possibility of genetically based refinements in diagnosis. However, the scores derived here have little value for individual risk prediction, meaning that application

to clinical genetic testing for schizophrenia would be unwarranted. In the future, measures of polygenic burden, along with known risk loci and non-genetic factors such as season of birth, life stress, obstetrical complications, viral infections and epigenetics, could open new avenues for studying gene–gene and gene–environment interactions.

Increasing the discovery sample size should substantially refine the polygenic scores derived here. The variance explained by the observed score increases from ~3% to over 20% in extended simulations of 20,000 case/control pairs, as will soon be available by international meta-analytic efforts such as the Psychiatric GWAS Consortium<sup>22–24</sup> (section 18 in Supplementary Information and Supplementary Fig. 8). Furthermore, analyses that focus on gene pathways, clinical features and non-additivity may increase the variance captured by the score and identify genes or biological systems that are either shared by, or unique to, schizophrenia and bipolar disorder.

We identified fewer unambiguously associated variants than studies of some non-psychiatric diseases of comparable size<sup>25</sup>. Nonetheless, for other diseases replicated variants typically account for only a modest fraction of risk. The nature of this ‘missing heritability’ is a general problem now faced by complex disease geneticists<sup>26</sup>. For schizophrenia, our data point to a genetic architecture that includes many common variants of small effect. The extent to which similar models characterize genetic variation within and across other complex diseases remains to be investigated.

## METHODS SUMMARY

Cases satisfied criteria for schizophrenia. Clinical characteristics and copy number variation have been described previously<sup>17</sup>. DNA was extracted from whole blood, with approval from institutional review boards. Genotypes were called using the Birdseed/Birdsuite algorithm<sup>27</sup> and analyses were performed with PLINK version 1.05 (ref. 28). Association analyses used a Cochran–Mantel–Haenszel test and logistic regression with covariates for sample site and ancestry. In the simulations, we generated data sets with pairs of unobserved variants and marker SNPs in varying degrees of within-pair linkage disequilibrium, on the basis of the effective number of independent SNPs in the ISC, and assuming Hardy–Weinberg equilibrium and linkage equilibrium between different pairs of SNPs. We considered a large grid of possible values for allele frequency and effect size distributions, also varying the proportion of non-null variants and the linkage disequilibrium between causal allele and observed marker. We retained models that produced similar profiles of target sample  $R^2$  compared to the original ISC analysis, for the same range of  $P_T$  thresholds, and calculated the indicated total genetic variance under these models, assuming additivity within and across loci. See Supplementary Information for details.

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Supplementary Information is linked to the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

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