Title: Genome-wide study identifies 611 loci associated with risk tolerance and risky behaviors

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Abstract:

Humans vary substantially in their willingness to take risks. In a combined sample of over one million individuals, we conducted genome-wide association studies (GWAS) of general risk tolerance, adventurousness, and risky behaviors in the driving, drinking, smoking, and sexual domains. We identified 611 approximately independent genetic loci associated with at least one of our phenotypes, including 124 with general risk tolerance. We report evidence of substantial shared genetic influences across general risk tolerance and risky behaviors: 72 of the 124 general risk tolerance loci contain a lead SNP for at least one of our other GWAS, and general risk tolerance is moderately to strongly genetically correlated ($|\hat{r}_g| \sim 0.25$ to 0.50) with a range of risky behaviors. Bioinformatics analyses imply that genes near general-risk-tolerance-associated SNPs are highly expressed in brain tissues and point to a role for glutamatergic and GABAergic neurotransmission. We find no evidence of enrichment for genes previously hypothesized to relate to risk tolerance.

Main Text:

Choices in important domains of life, including health, fertility, finance, employment, and social relationships, rarely have consequences that can be anticipated perfectly. The degree of variability in possible outcomes is called risk. Risk tolerance—defined as the willingness to take risks, typically to obtain some reward—varies substantially across humans and has been actively studied in the behavioral and social sciences. An individual's risk tolerance may vary across domains, but survey-based measures of *general* risk tolerance (e.g., "Would you describe yourself as someone who takes risks?") have been found to be good all-around predictors of risky behaviors such as portfolio allocation, occupational choice, smoking, drinking alcohol, and starting one's own business[1–3].

Twin studies have established that various measures of risk tolerance are moderately heritable ($h^2 \sim 30\%$, although estimates in the literature vary[3–5]). Discovery of specific genetic variants associated with general risk tolerance could advance our understanding of how genetic influences are amplified and dampened by environmental factors; provide insights into underlying biological pathways; enable the construction of polygenic scores (indexes of many genetic variants) that can be used as overall measures of genetic influences on individuals; and help distinguish genetic variation associated with general versus domain-specific risk tolerance.

Although risk tolerance has been one of the most studied phenotypes in social science genetics, most claims of positive findings have been based on small-sample candidate gene studies (**Supplementary Table 11.1**), whose limitations are now appreciated[6]. To date, only two loci associated with risk tolerance have been identified in genome-wide association studies (GWAS)[7,8].

Here, we report results from large-scale GWAS of self-reported general risk tolerance (our primary phenotype) and six supplementary phenotypes: "adventurousness" (defined as the self-reported tendency to be adventurous vs. cautious); four risky behaviors: "automobile speeding propensity" (the tendency to drive faster than the speed limit), "drinks per week" (the average number of alcoholic drinks consumed per week), "ever smoker" (whether one has ever been a smoker), and "number of sexual partners" (the lifetime number of sexual partners); and the first principal component (PC) of these four risky behaviors, which we interpret as capturing the general tendency to take risks across domains. All seven phenotypes are coded such that higher

phenotype values are associated with higher risk tolerance or risk taking. **Table 1** lists, for each GWAS, the datasets we analyzed and the GWAS sample size.

Association analyses

All seven GWAS were performed in European-ancestry subjects, following procedures described in a pre-specified analysis plan (https://osf.io/cjx9m/) and in **Supplementary Information section 2**.

In the discovery phase of our GWAS of general risk tolerance (n = 939,908), we performed a sample-size-weighted meta-analysis of results from the UK Biobank (UKB, n = 431,126) and a sample of research participants from 23andMe (n = 508,782). The UKB measure of general risk tolerance is based on the question: "Would you describe yourself as someone who takes risks? Yes / No." The 23andMe measure is based on a question about overall comfort taking risks, with five response options ranging from "very comfortable" to "very uncomfortable." The genetic correlation[9] between the UKB and 23andMe cohorts ($\hat{r}_g$ = 0.77, SE = 0.02) is smaller than one but high enough to justify our approach of pooling the two cohorts[10].

The Q-Q plot (**Extended Data Fig. 3.2a**) from the discovery GWAS exhibits substantial inflation (λ_{GC} = 1.41). According to the estimated intercept from a linkage disequilibrium (LD) Score regression[11], only a small share of this inflation (~5%) in test statistics is due to bias. To account for this bias, we inflated GWAS standard errors by the square root of the LD Score regression intercept.

We identified 124 approximately independent SNPs (pairwise $r^2 < 0.1$) that attained genome-wide significance ($P < 5\times10^{-8}$). These 124 "lead SNPs" are listed in **Supplementary Table 3.1** and shown in **Fig. 1a**. All have coefficients of determination (R^2's) below 0.02%, and the SNP with the largest per-allele effect is estimated to increase general risk tolerance by ~0.026 standard deviations in our discovery sample (**Extended Data Fig. 3.3**).

In the replication phase of our GWAS of general risk tolerance (combined n = 35,445), we meta-analyzed summary statistics from ten smaller cohorts. Additional details on cohort-level phenotype measures are provided in **Supplementary Table 1.2**. The questions differ in terms of their exact wording and number of response categories, but all questions ask subjects about their

overall or general attitudes toward risk. The genetic correlation[9] between the discovery and replication GWAS is 0.83 (SE = 0.13). 123 of the 124 lead SNPs were available or well proxied by an available SNP in the replication GWAS results. Out of the 123 SNPs, 94 have a concordant sign ($P = 1.7\times10^{-9}$) and 23 are significant at the 5% level in one-tailed t tests ($P = 4.5\times10^{-8}$) (**Extended Data Fig. 5.1**). This empirical replication record matches theoretical projections that take into account sampling variation and the winner's curse (**Supplementary Information section 5**).

Our six supplementary GWAS—of adventurousness, four risky behaviors, and their principal component (n = 315,894 to 557,923; **Supplementary Tables 1.1-1.2**)—were conducted using methods comparable to those in the primary GWAS, but without a replication phase. **Extended Data Fig. 3.2** (**c** to **h**) shows Q-Q plots and **Extended Data Fig. 3.1** (**a** to **f**) shows Manhattan plots.

Table 1 provides a summary overview of the seven GWAS. We identified a total of 865 lead SNPs across the seven GWAS. The lead SNPs are located in 611 approximately independent loci, where a locus is defined as the set of all SNPs in weak LD (pairwise $r^2 > 0.1$) with a lead SNP. The SNP heritabilities of the seven phenotypes range from ~0.05 (for general risk tolerance) to ~0.16 (for the first PC of the four risky behaviors).

Genetic overlap

There is substantial overlap across the results of our GWAS. For example, 72 of the 124 general-risk-tolerance lead SNPs are in loci that also contain lead SNPs for at least one of the other GWAS, including 45 for adventurousness and 49 for at least one of the four risky behaviors or their first PC. To empirically assess if this overlap could be attributed to chance, we conducted a resampling exercise under the null hypothesis that the lead SNPs of our supplementary GWAS are distributed independently of the 124 general-risk-tolerance lead loci. We strongly rejected this null hypothesis ($P < 0.0001$; **Supplementary Information section 3.3.3**).

Several regions of the genome stand out for being associated both with general risk tolerance and with all or most of the supplementary phenotypes. We tested whether the signs of the lead SNPs located in these regions tend to be concordant across our primary and supplementary GWAS. We

strongly rejected the null hypothesis of no concordance ($P < 3\times10^{-30}$; **Supplementary Information section 3.2.3**), suggesting that these regions represent shared genetic influences, rather than colocalization of causal SNPs. **Fig. 1b** and **Extended Data Fig. 3.4** show local Manhattan plots for some of these regions. The long-range LD region[12] on chromosome 3 (~83.4 to 86.9 Mb) contains lead SNPs from all seven GWAS as well as the most significant lead SNP from the general risk tolerance GWAS, rs993137 ($P = 2.14\times10^{-40}$), which is located in the gene *CADM2*. Another long-range LD region, on chromosome 6 (~25.3 to 33.4 Mb), covers the HLA-complex and contains lead SNPs from all GWAS except drinks per week. Three candidate inversions (i.e., genomic regions that are highly prone to inversion polymorphisms; **Supplementary Information section 2.9.2**) on chromosomes 7 (~124.6 to 132.7 Mb), 8 (~7.89 to 11.8 Mb), and 18 (~49.1 to 55.5 Mb) contain lead SNPs from six, five, and all seven of our GWAS, respectively. Finally, four other LD blocks[13] that do not overlap known long-range LD or candidate inversion regions each contain lead SNPs from five of our GWAS (including general risk tolerance). The two long-range LD regions and the three candidate inversions have previously been found to be associated with numerous phenotypes, including many cognitive and neuropsychiatric phenotypes[14].

To investigate genetic overlap at the genome-wide level, we estimated genetic correlations with self-reported general risk tolerance using bivariate LD Score regression[9]. (For this and all subsequent analyses involving general risk tolerance, we used the summary statistics from the combined meta-analysis of our discovery and replication GWAS.) The estimated genetic correlations with our six supplementary phenotypes are all positive, larger than ~0.25, and highly significant ($P < 2.3\times10^{-30}$; **Fig. 2**), indicating that SNPs associated with higher general risk tolerance also tend to be associated with riskier behavior. The largest estimated genetic correlations are with adventurousness ($\hat{r}_g = 0.83$, $SE = 0.01$), number of sexual partners (0.52, $SE = 0.02$), automobile speeding propensity (0.45, $SE = 0.02$), and the first PC of the four risky behaviors (0.50, $SE = 0.02$).

Our estimates of the genetic correlations between general risk tolerance and the supplementary risky behaviors are substantially higher than the corresponding phenotypic correlations (**Supplementary Tables 1.3** and **7.1**). Although measurement error partly accounts for the low phenotypic correlations, the genetic correlations remain considerably higher even after

138 adjustment of the phenotypic correlations for measurement error. The comparatively large
139 genetic correlations support the view that a general factor of risk tolerance partly accounts for
140 cross-domain variation in risky behavior[15,16] and imply that this factor is genetically influenced.
141 The lower phenotypic correlations suggest that environmental factors are more important
142 contributors to domain-specific risky behavior[17,18].

143 To increase the precision of our estimates of the SNPs' effects on general risk tolerance, we
144 leveraged the high degree of genetic overlap across our phenotypes by conducting Multi-Trait
145 Analysis of GWAS (MTAG)[19]. We used as inputs the summary statistics of our GWAS of
146 general risk tolerance, of our first five supplementary GWAS (i.e., not including the first PC of
147 the four risky behaviors), and of a previously published GWAS on lifetime cannabis use[20]
148 (**Supplementary Information section 9**). MTAG increased the number of general-risk-tolerance
149 lead SNPs from 124 to 312 (**Extended Data Fig. 9.1**, **Supplementary Table 9.1**).

150 We also estimated genetic correlations between general risk tolerance and 28 additional
151 phenotypes (**Fig. 2** and in **Supplementary Table 7.1**). These included phenotypes for which we
152 could obtain summary statistics from previous GWAS, as well as five phenotypes for which we
153 conducted new GWAS. The estimated genetic correlations for the personality traits extraversion
154 ($\hat{r}_g$ = 0.51, *SE* = 0.03), neuroticism (-0.42, *SE* = 0.04), and openness to experience (0.33, *SE* =
155 0.03) are substantially larger in magnitude than previously reported phenotypic correlations[21],
156 pointing to substantial shared genetic influences among general risk tolerance and these traits.
157 After Bonferroni correction, we also find significant positive genetic correlations with the
158 neuropsychiatric phenotypes ADHD, bipolar disorder, and schizophrenia. Viewed in light of the
159 genetic correlations we find with risky behaviors classified as externalizing (e.g., substance use,
160 elevated sexual behavior, and fast driving), these results suggest the hypothesis that the overlap
161 with the neuropsychiatric phenotypes is driven by their externalizing component.

162

163 Biological annotation

164 To gain insights into the biological mechanisms through which genetic variation influences
165 general risk tolerance, we conducted a number of analyses. First, we systematically reviewed the
166 literature that aimed to link risk tolerance to biological pathways (**Supplementary Information**
167 **section 11**). Our review covered studies based on candidate genes (i.e., specific genetic variants

168 used as proxies for biological pathways), pharmacological manipulations, biochemical assays,
169 genetic manipulations in rodents, as well as other research designs. Our review identified 132
170 articles that matched our search criteria (**Supplementary Table 11.1**).

171 Previous work has focused on five main biological pathways: the steroid hormone cortisol, the
172 monoamines dopamine and serotonin, and the steroid sex hormones estrogen and testosterone.
173 Using a MAGMA[22] competitive gene-set analysis, we found no evidence that SNPs within genes
174 associated with these five pathways tend to be more associated with general risk tolerance than
175 SNPs in other genes (**Supplementary Table 11.3**). Further, none of the other bioinformatics
176 analyses we report below point to these pathways.

177 We also examined the 15 most commonly tested autosomal genes within the dopamine and
178 serotonin pathways, which were the focus of most of the 34 candidate-gene studies identified by
179 our literature review. We verified that the SNPs available in our GWAS results tag most of the
180 genetic variants typically used to test the 15 genes. Across one SNP-based test and two gene-
181 based tests, we found no evidence of non-negligible associations between those genes and
182 general risk tolerance (**Fig. 1c** and **Supplementary Table 11.4**). (We note, however, that some
183 brain regions identified in analyses we report below are areas where dopamine and serotonin
184 play important roles.)

185 Second, we performed a MAGMA[22] gene analysis to test each of ~18,000 protein-coding genes
186 for association with general risk tolerance (**Supplementary Information section 12.2**). After
187 Bonferroni correction, 285 genes were significant (**Extended Data Fig. 12.1** and
188 **Supplementary Table 12.3**). To gain insight into the functions and expression patterns of these
189 285 genes, we looked up these genes in the Gene Network[23] co-expression database. Third, to
190 identify relevant biological pathways and identify tissues in which genes near general-risk-
191 tolerance-associated SNPs are expressed, we applied the software tool DEPICT[24] to the SNPs
192 with P values less than 10^{-5} in our GWAS of general risk tolerance (**Supplementary**
193 **Information section 12.4**).

194 Both the Gene Network and the DEPICT analyses separately point to a role for glutamate and
195 GABA neurotransmitters, which are the main excitatory and inhibitory neurotransmitters in the
196 brain, respectively[25] (**Fig. 3a** and **Supplementary Tables 12.4** and **12.8**). To our knowledge, no
197 published large-scale GWAS of cognition, personality, or neuropsychiatric phenotypes has

198 pointed to clear roles both for glutamate and GABA (although glutamatergic neurotransmission
199 has been implicated in recent GWAS of schizophrenia[26] and major depression[27]). Our results
200 suggest that the balance between excitatory and inhibitory neurotransmission may contribute to
201 variation in general risk tolerance across individuals.

202 The Gene Network and the DEPICT tissue enrichment analyses also both separately point to
203 enrichment of the prefrontal cortex and the basal ganglia (**Fig. 3b** and **Supplementary Tables**
204 **12.4**, **12.6**, and **12.7**). The cortical and subcortical regions highlighted by DEPICT include some
205 of the major components of the cortical-basal ganglia circuit, which is known as the reward
206 system in human and non-human primates and is critically involved in learning, motivation, and
207 decision-making, notably under risk and uncertainty[28,29]. We caution, however, that our results
208 do not point exclusively to the reward system.

209 Lastly, we used stratified LD Score regression[30] to test for the enrichment of SNPs associated
210 with histone marks in 10 tissue or cell types (**Supplementary Information section 12.1**).
211 Central nervous system tissues are the most enriched, accounting for 44% (*SE* = 3%) of the
212 heritability while comprising only 15% of the SNPs (**Extended Data Fig. 12.3a** and
213 **Supplementary Table 12.2**). Immune/hematopoietic tissues are also significantly enriched.
214 While a role for the immune system in modulating risk tolerance is plausible given prior
215 evidence of its involvement in several neuropsychiatric disorders[26,27], future work is needed to
216 confirm this result and to uncover specific pathways that might be involved.

217

218 Polygenic prediction

219 We constructed polygenic scores of general risk tolerance to gauge their potential usefulness in
220 empirical research (**Supplementary Information section 10**). We used the Add Health, HRS,
221 NTR, STR, UKB-siblings, and Zurich cohorts as validation cohorts (**Supplementary Table 1.1**
222 provides an overview of these cohorts; the UKB-siblings cohort comprised individuals with at
223 least one full sibling in the UKB). For each validation cohort, we constructed the score using
224 summary statistics from a meta-analysis of our discovery and replication GWAS that excluded
225 the cohort. Our measure of predictive power is the incremental R^2 (or pseudo-R^2) from adding
226 the score to a regression of the phenotype on sex, birth year, and the top ten principal
227 components of the genetic relatedness matrix.

228 Our preferred score was constructed with LDpred[31]. In the UKB-siblings cohort, which is our
229 largest validation cohort ($n \sim 35{,}000$), the score's predictive power is 1.6% for general risk
230 tolerance, 1.0% for the first PC of the four risky behaviors, 0.8% for number of sexual partners,
231 0.6% for automobile speeding propensity, and ~0.15% for drinks per week and ever smoker.
232 Across our validation cohorts, the score is also predictive of several personality phenotypes and a
233 suite of real-world measures of risky behaviors in the health, financial, career, and other domains
234 (**Extended Data Figs. 10.1-10.2** and **Supplementary Tables 10.1-10.3**). The incremental R^2 we
235 observe for general risk tolerance is consistent with the theoretical prediction, given the SNP
236 heritability of general risk tolerance (**Table 1**) and the imperfect genetic correlations across the
237 GWAS and validation cohorts[32,33] (**Supplementary Information section 10.4**).

238

239 Discussion

240 Our results provide insights into biological mechanisms that influence general risk tolerance. Our
241 bioinformatics analyses point to the role of gene expression in brain regions that have been
242 identified by neuroscientific studies on decision-making, notably the prefrontal cortex, basal
243 ganglia, and midbrain, thereby providing convergent evidence with that from neuroscience[28,29].
244 Yet our analyses failed to find evidence for the main biological pathways that had been
245 previously hypothesized to influence risk tolerance. Instead, our analyses implicate genes
246 involved in glutamatergic and GABAergic neurotransmission, which were heretofore not
247 generally believed to play a role in risk tolerance.

248 Although our focus has been on the genetics of general risk tolerance and risky behaviors,
249 environmental and demographic factors account for a substantial share of these phenotypes'
250 variation. We observe sizeable effects of sex and age on general risk tolerance in the UKB data
251 (**Extended Data Fig. 1.1**), and life experiences have been shown to affect both measured risk
252 tolerance and risky behaviors (e.g., refs. 34,35). The data we have generated will allow
253 researchers to construct and use polygenic scores of general risk tolerance to measure how
254 environmental, demographic, and genetic factors interact with one another.

255 For the behavioral sciences, our results bear on the ongoing debate about the extent to which risk
256 tolerance is a "domain-general" as opposed to a "domain-specific" trait. Low phenotypic
257 correlations in risk tolerance across decision-making domains have been interpreted as

258 supporting the domain-specific view[17,18]. Across the risky behaviors we study, we find that the
259 genetic correlations are considerably higher than the phenotypic correlations (even after the latter
260 are corrected for measurement error) and that many lead SNPs are shared across our phenotypes.
261 These observations suggest that the low phenotypic correlations across domains are due to
262 environmental factors that dilute the effects of a genetically-influenced domain-general factor of
263 risk tolerance.

264 **References:**

265 1. Dohmen, T. *et al.* Individual risk attitudes: Measurement, determinants, and behavioral
266 consequences. *J. Eur. Econ. Assoc.* **9,** 522–550 (2011).
267 2. Falk, A., Dohmen, T., Falk, A. & Huffman, D. The nature and predictive power of
268 preferences: Global evidence. *IZA Discussion Papers* (2015).
269 3. Beauchamp, J. P., Cesarini, D. & Johannesson, M. The psychometric and empirical
270 properties of measures of risk preferences. *J. Risk Uncertain.* **54,** 203–237 (2017).
271 4. Cesarini, D., Dawes, C. T., Johannesson, M., Lichtenstein, P. & Wallace, B. Genetic
272 variation in preferences for giving and risk taking. *Q. J. Econ.* **124,** 809–842 (2009).
273 5. Harden, K. P. *et al.* Beyond dual systems: A genetically-informed, latent factor model of
274 behavioral and self-report measures related to adolescent risk-taking. *Dev. Cogn.*
275 *Neurosci.* **25,** 221–234 (2017).
276 6. Hewitt, J. K. Editorial policy on candidate gene association and candidate gene-by-
277 environment interaction studies of complex traits. *Behav. Genet.* **42,** 1–2 (2012).
278 7. Day, F. R. *et al.* Physical and neurobehavioral determinants of reproductive onset and
279 success. *Nat. Genet.* **48,** 617–623 (2016).
280 8. Strawbridge, R. J. *et al.* Genome-wide analysis of risk-taking behaviour and cross-
281 disorder genetic correlations in 116 255 individuals from the UK Biobank cohort. *bioRxiv*
282 (2017). doi:http://dx.doi.org/10.1101/177014
283 9. Bulik-Sullivan, B. K. *et al.* An atlas of genetic correlations across human diseases and
284 traits. *Nat. Genet.* **47,** 1236–1241 (2015).
285 10. Okbay, A. *et al.* Genetic variants associated with subjective well-being, depressive
286 symptoms, and neuroticism identified through genome-wide analyses. *Nat. Genet.* **48,**
287 624–633 (2016).
288 11. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from
289 polygenicity in genome-wide association studies. *Nat. Genet.* **47,** 291–295 (2015).
290 12. Price, A. L. *et al.* Long-range LD can confound genome scans in admixed populations.
291 *Am. J. Hum. Genet.* **83,** 132–139 (2008).
292 13. Berisa, T. & Pickrell, J. K. Approximately independent linkage disequilibrium blocks in
293 human populations. *Bioinformatics* **32,** 283–285 (2016).
294 14. Welter, D. *et al.* The NHGRI GWAS Catalog, a curated resource of SNP-trait

295 associations. *Nucleic Acids Res.* **42,** D1001-1006 (2014).
296 15. Einav, B. L., Finkelstein, A., Pascu, I. & Cullen, M. R. How general are risk preferences?
297 Choices under uncertainty in different domains. *Am. Econ. Rev.* **102,** 2606–2638 (2016).
298 16. Frey, R., Pedroni, A., Mata, R., Rieskamp, J. & Hertwig, R. Risk preference shares the
299 psychometric structure of major psychological traits. *Sci. Adv.* **3,** e1701381 (2017).
300 17. Weber, E. U., Blais, A. E. & Betz, N. E. A domain-specific risk-attitude scale: Measuring
301 risk perceptions and risk behaviors. *J. Behav. Decis. Mak. J. Behav. Dec. Mak.* **15,** 263–
302 290 (2002).
303 18. Hanoch, Y., Johnson, J. G. & Wilke, A. Domain specificity in experimental measures and
304 participant recruitment: an application to risk-taking behavior. *Psychol. Sci.* **17,** 300–304
305 (2006).
306 19. Turley, P. *et al.* MTAG: Multi-Trait Analysis of GWAS. *bioRxiv* (2017).
307 doi:https://doi.org/10.1101/118810
308 20. Stringer, S. *et al.* Genome-wide association study of lifetime cannabis use based on a large
309 meta-analytic sample of 32 330 subjects from the International Cannabis Consortium.
310 *Transl. Psychiatry* **6,** e769 (2016).
311 21. Becker, A., Deckers, T., Dohmen, T., Falk, A. & Kosse, F. The relationship between
312 economic preferences and psychological personality measures. *Annu. Rev. Econom.* **4,**
313 453–478 (2012).
314 22. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: Generalized gene-
315 set analysis of GWAS data. *PLoS Comput. Biol.* **11,** 1–19 (2015).
316 23. Fehrmann, R. S. N. *et al.* Gene expression analysis identifies global gene dosage
317 sensitivity in cancer. *Nat. Genet.* **47,** 115–125 (2015).
318 24. Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using
319 predicted gene functions. *Nat. Commun.* **6,** 5890 (2015).
320 25. Petroff, O. A. C. GABA and glutamate in the human brain. *Neurosci.* **8,** 562–573 (2002).
321 26. Ripke, S. *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature*
322 **511,** 421–427 (2014).
323 27. Wray, N. R. *et al.* Genome-wide association analyses identify 44 risk variants and refine
324 the genetic architecture of major depression. *bioRxiv* (2017).
325 doi:https://doi.org/10.1101/167577

326 28. Haber, S. N. & Knutson, B. The reward circuit: linking primate anatomy and human
327 imaging. *Neuropsychopharmacology* **35,** 4–26 (2010).
328 29. Tobler, P. N. & Weber, E. U. Valuation for Risky and Uncertain Choices. in
329 *Neuroeconomics* 149–172 (Elsevier, 2014). doi:10.1016/B978-0-12-416008-8.00009-7
330 30. Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-
331 wide association summary statistics. *Nat. Genet.* **47,** 1228–1235 (2015).
332 31. Vilhjálmsson, B. J. *et al.* Modeling linkage disequilibrium increases accuracy of polygenic
333 risk scores. *Am. J. Hum. Genet.* **97,** 576–592 (2015).
334 32. Daetwyler, H. D., Villanueva, B. & Woolliams, J. A. Accuracy of predicting the genetic
335 risk of disease using a genome-wide approach. *PLoS One* **3,** e3395 (2008).
336 33. de Vlaming, R. *et al.* Meta-GWAS Accuracy and Power (MetaGAP) calculator shows that
337 hiding heritability is partially due to imperfect genetic correlations across studies. *PLoS*
338 *Genet.* **13,** e1006495 (2017).
339 34. Sahm, C. R. How much does risk tolerance change? *Q. J. Financ.* **2,** 1250020 (2012).
340 35. Malmendier, U. & Nagel, S. Depression babies: Do macroeconomic experiences affect
341 risk taking? *Q. J. Econ.* **126,** 373–416 (2011).
342 36. Frey, B. J. & Dueck, D. Clustering by passing messages between data points. *Science*
343 **315,** (2007).
344 37. Furberg, H. *et al.* Genome-wide meta-analyses identify multiple loci associated with
345 smoking behavior. *Nat. Genet.* **42,** 441–447 (2010).
346 38. Shi, H., Kichaev, G. & Pasaniuc, B. Contrasting the genetic architecture of 30 complex
347 traits from summary association data. *Am. J. Hum. Genet.* **99,** 139–153 (2016).
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Author Contributions A full list of author contributions is included in **Supplementary Information section 13**.

Author Information Adam Auton, Pierre Fontanillas, David A Hinds, and Aaron Kleinman are employees of 23andMe, and Ronald Kessler has had ties to various companies in the past three years; the authors declare no other competing financial interests. Further details are provided in **Supplementary Information section 13**. Correspondence and requests for materials should be addressed to J.P.B (jonathan.pierre.beauchamp@gmail.com), R.K.L. (r.karlssonlinner@vu.nl), D.J.B (daniel.benjamin@gmail.com) or P.D.K. (p.d.koellinger@vu.nl).

Data Availability Upon publication, results can be downloaded from the SSGAC website (http://thessgac.org/data).

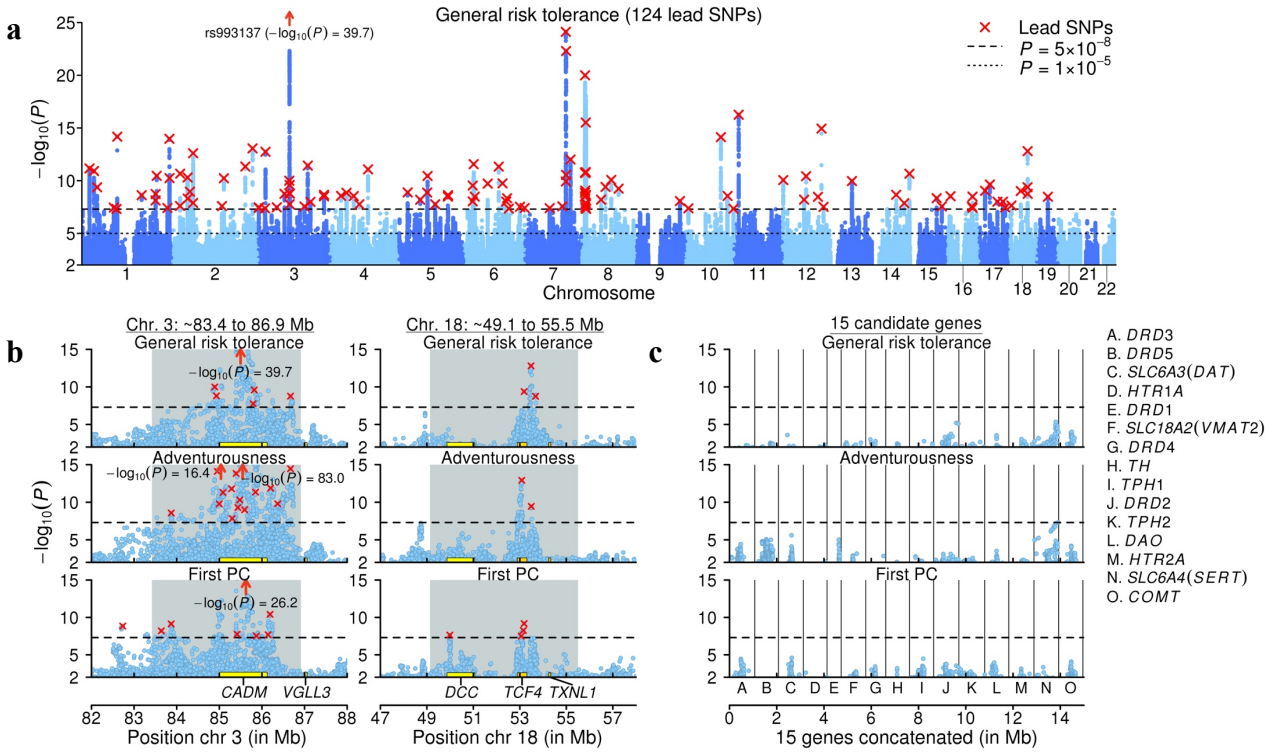

Figure 1 | Manhattan plots. In all panels, the *x*-axis is chromosomal position; the *y*-axis is the significance on a $-\log_{10}$ scale; the horizontal dashed line marks the threshold for genome-wide significance ($P = 5\times10^{-8}$); and each approximately independent (pairwise $r^2 < 0.1$) genome-wide significant association ("lead SNP") is marked by a red ×. **a**, Manhattan plots for the discovery GWAS of general risk tolerance. **b**, Local Manhattan plots of two genomic regions that contain lead SNPs for all seven of our GWAS. The gray background marks the locations of long-range LD or candidate inversion regions. **c**, Local Manhattan plots of the loci around the 15 most commonly tested candidate genes in the prior literature on the genetics of risk tolerance. Each locus comprises all SNPs within 500 kb of the gene's borders that are in LD ($r^2 > 0.1$) with a SNP in the gene. The 15 plots are concatenated and shown together in the panel, divided by the black vertical lines. The 15 genes are not particularly strongly associated with general risk tolerance or the risky behaviors, as can be seen by comparing the results within each row across panels **b** and **c** (the three rows correspond to the GWAS of general risk tolerance, adventurousness, and the first PC of the four risky behaviors).

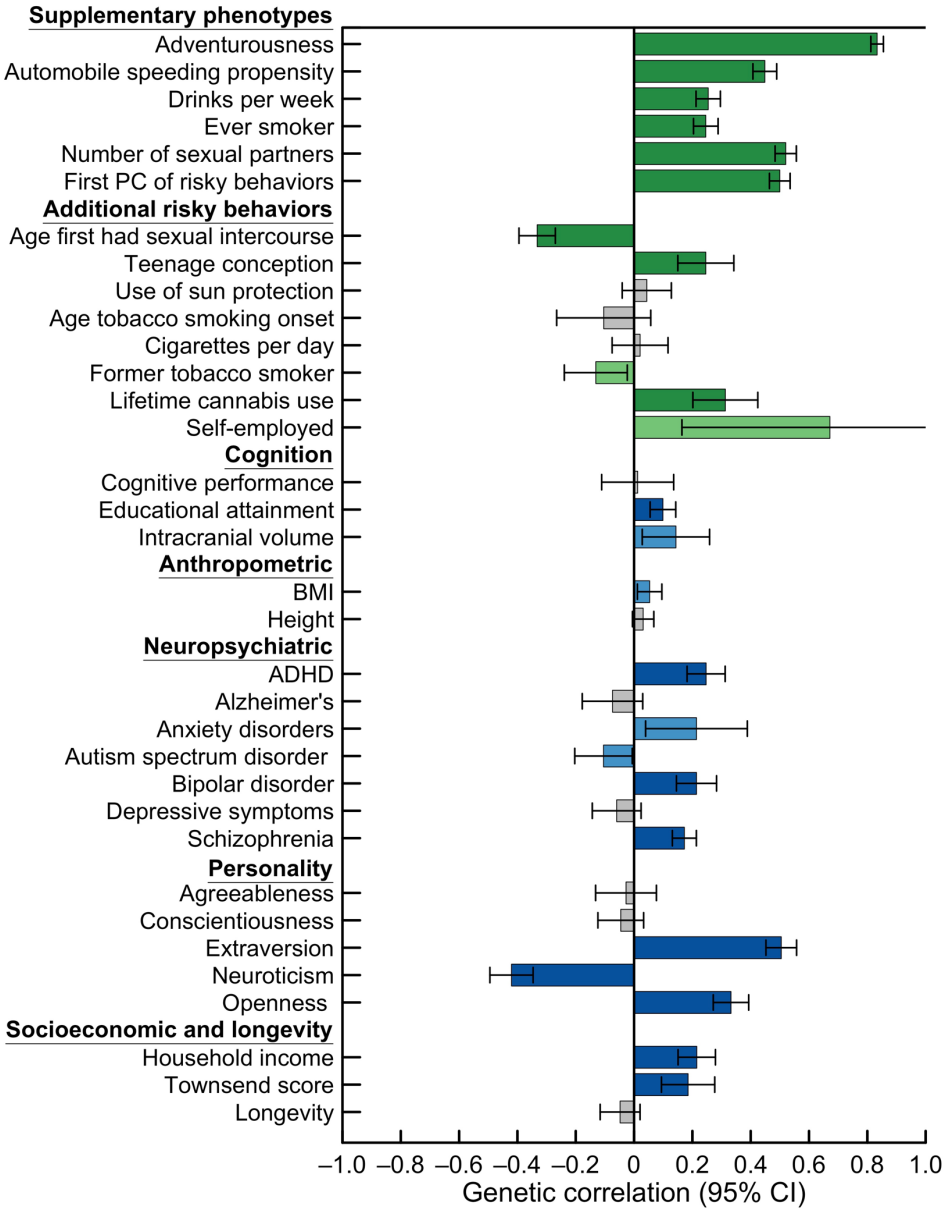

Figure 2 | Genetic correlations with general risk tolerance. The genetic correlations were estimated using bivariate LD Score (LDSC) regression[9]. Error bars show 95% confidence intervals. For the supplementary phenotypes and the additional risky behaviors, green bars represent significant estimates with the expected signs, where higher risk tolerance is associated with riskier behavior. For the other phenotypes, blue bars represent significant estimates. Light green and light blue bars represent genetic correlations that are statistically significant at the 5% level, and dark green and dark blue bars represent correlations that are statistically significant after Bonferroni correction for 34 tests (the total number of phenotypes tested). Grey bars represent correlations that are not statistically significant at the 5% level.

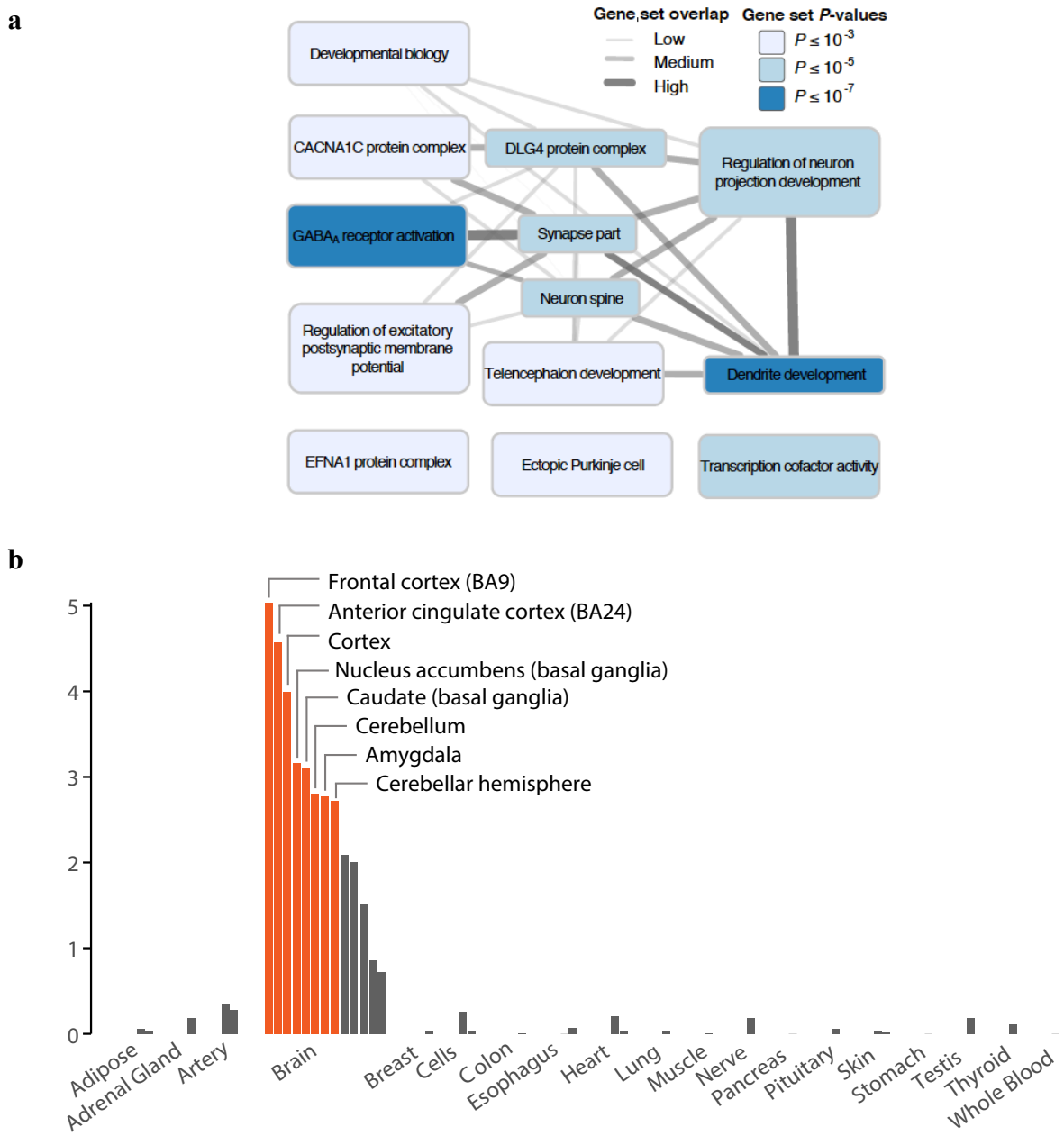

Figure 3 | Results from selected biological analyses. a, DEPICT gene-set enrichment diagram. We identified 93 reconstituted gene sets that are significantly enriched (FDR < 0.01) for genes overlapping loci associated with general risk tolerance; using the Affinity Propagation method[36], these were grouped into the 13 clusters displayed in the graph. Each cluster was named after the most significant gene set it contained, and each cluster's color represents the permutation *P* value of its most significant gene set. The "synapse part" cluster includes the gene set "glutamate receptor activity," and several members of the "$GABA_A$ receptor activation" cluster are defined by gamma-aminobutyric acid signaling. Overlap between the named representatives of two

clusters is represented by an edge. Edge width represents the Pearson correlation ρ between the two respective vectors of gene membership scores ($\rho < 0.3$, no edge; $0.3 \leq \rho < 0.5$, thin edge; $0.5 \leq \rho < 0.7$, intermediate edge; $\rho \geq 0.7$, thick edge). **b**, Results of DEPICT tissue enrichment analysis using GTEx data. The panel shows whether the genes overlapping loci associated with general risk tolerance are significantly overexpressed (relative to genes in random sets of loci matched by gene density) in various tissues. Tissues are grouped by organ or tissue type. The orange bars correspond to tissues with significant overexpression (FDR < 0.01). The *y*-axis is the significance on a $-\log_{10}$ scale.

Table 1 | GWAS results

GWAS	Cohorts analyzed	*n*	Mean χ^2	LD Score intercept (*SE*)	# lead SNPs	SNP h^2 (*SE*)
General risk tolerance (disc. GWAS)	UKB; 23andMe	939,908	1.85	1.04 (0.01)	124	0.046 (0.001)
General risk tolerance (rep. GWAS)	10 indep. cohorts	35,445	1.03	1.00 (0.07)	0	--
General risk tolerance (disc. + rep.)	UKB; 23andMe; 10 indep. cohorts	975,353	1.87	1.04 (0.01)	132	0.045 (0.001)
Adventurousness	23andMe	557,923	1.98	1.05 (0.01)	167	0.098 (0.002)
Automobile speeding propensity	UKB	404,291	1.53	1.03 (0.01)	42	0.079 (0.003)
Drinks per week	UKB	414,343	1.61	1.03 (0.01)	85	0.085 (0.003)
Ever smoker	UKB; TAG Consortium [37]	518,633	1.97	1.05 (0.01)	223	0.109 (0.003)
Number of sexual partners	UKB	370,711	1.77	1.04 (0.01)	118	0.128 (0.003)
First PC of the four risky behaviors	UKB	315,894	1.77	1.05 (0.01)	106	0.156 (0.004)

The table provides an overview of the GWAS of our primary and supplementary phenotypes. "*n*": GWAS sample size; "Mean χ^2": mean GWAS chi-squared statistics across HapMap3 SNPs with minor allele frequency (MAF) greater than 0.01; "LD Score intercept": estimate of the intercept from a LD Score regression[11] using HapMap3 SNPs with MAF greater than 0.01; "# lead SNPs": number of lead SNPs, calculated after the associated statistics have been adjusted using the estimated LD score intercept; "SNP h^2": SNP heritability estimated with the Heritability Estimator from Summary Statistics (HESS) method[38] using 1000 Genomes phase 3 SNPs with MAF greater than 0.05; "disc.": discovery; "rep.": replication; "indep.": independent.

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