Unravelling the genetic architecture of musical rhythm: a large-scale genome-wide association study of beat synchronization

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Abstract

Moving in synchrony to a musical beat is a fundamental component of musicality. Here, we conducted a genome-wide association study (GWAS) to identify common genetic variants associated with beat synchronization in 606,825 individuals. Beat synchronization exhibited a highly polygenic architecture, with sixty-seven loci reaching genome-wide significance ($p<5x10^{-8}$) and SNP-based heritability (on the liability scale) of 13%-16%. Heritability was enriched for genes expressed in brain tissues, and for fetal and adult brain-specific gene regulatory elements, underscoring the role of central nervous system biomarkers linked to the genetic basis of the trait. We performed validations of the self-report phenotype (through internet-based experiments) and of the GWAS (polygenic scores for beat synchronization were associated with patients algorithmically classified as musicians in medical records of a separate biobank). Genetic correlations with breathing function, motor function, processing speed, and chronotype suggest shared genetic architecture with beat synchronization and provide avenues for new phenotypic and genetic explorations.

Introduction

Our tendency to perceive, create, and appreciate rhythms in a variety of contexts (e.g., speech, music, movement) is a feature of the human experience[1–3]. Rhythmic patterns provide predictable and robust sensorimotor structure to human interactions[4,5], helping guide our attention to communicatively important moments in time[6,7]. Even very young children are sensitive to the social and linguistic signals carried by rhythm[8–10], thus it is not surprising that parents use rhythmic vocalizations and synchronous movement (e.g., lullabies and rocking) to interact with their infants from birth[11,12]. Rhythmic musical interactions in young children and across the lifespan[13] are structured around the percept of a stable periodic pulse, termed the "beat" in Western music and also present in music of other cultures[1,14] (though different musical cultures varies in the way they incorporate beats in musical structure; see[15,16]). While music in general and rhythmic structures in particular significantly vary from one culture to another[16–18], there is preliminary evidence that hierarchical beat structure of most music is robust to cultural transmission[2] and indeed common in many types of music[1].

Beat perception and synchronization (i.e. perceiving, predicting, and moving predictively in synchrony to a musical beat[19]) is an important feature of musical experiences across many human cultures and musical genres[1,20]. The predictive temporal mechanisms afforded by beat structure enhance general perceptual and learning processes in music, including melody perception and production, singing, and joint music-making[3,6]. Recent work showed that some features of rhythm perception and production (e.g., categorical rhythm perception) varies across listeners from different cultures[14,20–22], the same studies showed considerable consistencies across cultures for

other features (for example preference for beat-based isochrony). Beat synchronization, and musicality in general, appear to have broad implications for society by supporting pro-social behavior[11,23] and well-being[24]. Many have proposed that beat perception and synchronization evolved in humans to support communication and group cohesion[19,25–27].

Neuroimaging findings have highlighted auditory-motor networks in the brain underlying rhythm perception and production[28], during which there is precise entrainment of neural oscillatory activity to musical signals, primarily involving motor planning areas and auditory regions of the brain, even during simple passive listening to music[29]. Neural mechanisms of entrainment, prediction, and reward work in concert to coordinate the timing of beat-related expectancies to musical signals during listening, playing, singing, and dance[27].

Although most people are able to effortlessly detect and synchronize with the beat even without musical training[4,19], there is still substantial inter-individual variability, *within* cultures, in the extent to which individuals can perceive and produce musical rhythms accurately[30,31], including the temporal precision of coordinating movement with a musical beat[32]. These individual differences could be due in part to genetic variation, and thus genetic approaches can be used to gain a foothold on the biological basis of musicality in humans (with the definition of *musicality* broadly encompassing musical behavior, music engagement and musical skill per[25]). Indeed, twin-modelling and other family-based studies point to moderate heritability of rhythm-related traits such as duration discrimination[33,34], rhythm discrimination[35], isochronous sensori-motor production[36], and off-beat detection[37]. Much less is known at the molecular level about

105 human genome variation underlying musicality[38] which to date has been investigated in
106 relatively small samples[34], due to the challenge of assessing musicality phenotypes in
107 samples large enough to provide sufficient power to detect common variants with small
108 effects (as expected for complex traits[39]). Large-scale genome-wide association studies
109 (GWAS) of musicality traits are thus needed to advance this field.

110 Our understanding of the biological underpinnings of beat synchronization, from
111 its genetic architecture to its neural instantiation and behavioral manifestation, requires
112 complex multi-methodological approaches. For instance, post-GWAS approaches (i.e.,
113 heritability enrichment of gene expression in central nervous tissues) can eventually be
114 used to illuminate the relationship between the genetic architecture of music-related
115 traits and patterns of neural activity reported in neuroscience studies.

116 Human tendencies to engage with music are beyond recreational; individual
117 differences in beat perception and synchronization abilities and the strength of neural
118 resources associated with rhythm are predictive of language and literacy skills[40,41] and
119 are more generally related to cognition, motor function, and social coordination[42]. The
120 underlying genetic architecture of beat synchronization may have clinical-translational
121 relevance, both for characterizing risk (i.e. atypical or impaired rhythm appears to be
122 associated with developmental speech-language disorders[43]) and for rhythm-based
123 rehabilitation (i.e. for stroke and Parkinson's[44]; with other promising benefits of music on
124 health under investigation[45]). Applying advanced genetic epidemiology methods[46] to
125 musicality phenotypes data collected in large population samples will generate new
126 avenues of research, allowing us to examine to what extent beat synchronization might

127 share genetic architecture with other traits, thus also highlighting common risk or
128 protective effects with other health and cognitive traits.
129
130 *Summary of Approach.*
131 Here, we report a novel genome-wide interrogation of beat synchronization. Our
132 approach was as follows: 1) We validated a subjective self-reported beat
133 synchronization item ("Can you clap in time with a musical beat?", referred to in this
134 paper as the "target item"), in relation to measured beat synchronization and rhythm
135 perception task performance, as a scalable and accurate phenotype for large-scale
136 population-based studies. 2) We identified genomic loci and established a polygenic
137 model of beat synchronization. We first conducted a genome-wide association study
138 (GWAS) to identify common genetic variants associated with beat synchronization in
139 606,825 individuals participating in research with the personal genetics company
140 23andMe, Inc. We then validated the findings in a separate genetic sample associated
141 with musicality in a health care context (in Vanderbilt's BioVU database), by testing
142 whether a cumulative sum of the genetic effects for beat synchronization detected in our
143 GWAS (i.e., polygenic score), was significantly associated with algorithmically identified
144 musicianship. We also estimated how much of the total phenotypic variance of beat
145 synchronization could be explained by all variation across the genome (i.e., SNP-based
146 heritability). 3) We further investigated the genetic architecture of beat synchronization,
147 using partitioned heritability and gene set enrichment analyses, with a particular focus
148 on genes that play a role in the central nervous system. We also evaluated the
149 contribution to beat synchronization of genomic regions that have experienced

150 significant human-specific evolutionary shifts (since the divergence of humans and
151 chimpanzees from their last common ancestor). 4) We explored shared genetic effects
152 (pleiotropy) on beat synchronization and other traits, performing exploratory genetic
153 correlation analysis including 764 complex traits for which a well-powered GWAS has
154 been performed and deposited in LDHub[47]. We then used genomic Structural Equation
155 Modelling (SEM) to characterize the relationship among the top associations between
156 beat synchronization and health-related traits. Findings were further investigated on the
157 phenotypic level in a separate experiment.
158

Results

Overview. Validating the self-reported beat synchronization phenotype

In light of prior work suggesting that musicality and rhythm skills are complex traits that can be quantified with both objective (experiment-derived) assessment and subjective self-reported data[48,49], we performed a series of validations of the self-report beat synchronization item (i.e., the single item “Can you clap in time with a music beat?” that was used in the genetic study), in relation to measured rhythm perception and beat production tasks. Both studies were administered in English for consistency. We also explored the relationship between task-based beat synchronization ability, a self-reported rhythm scale (from additional questionnaire items), and musicality. Study overviews and key results are summarized in Figure 1.

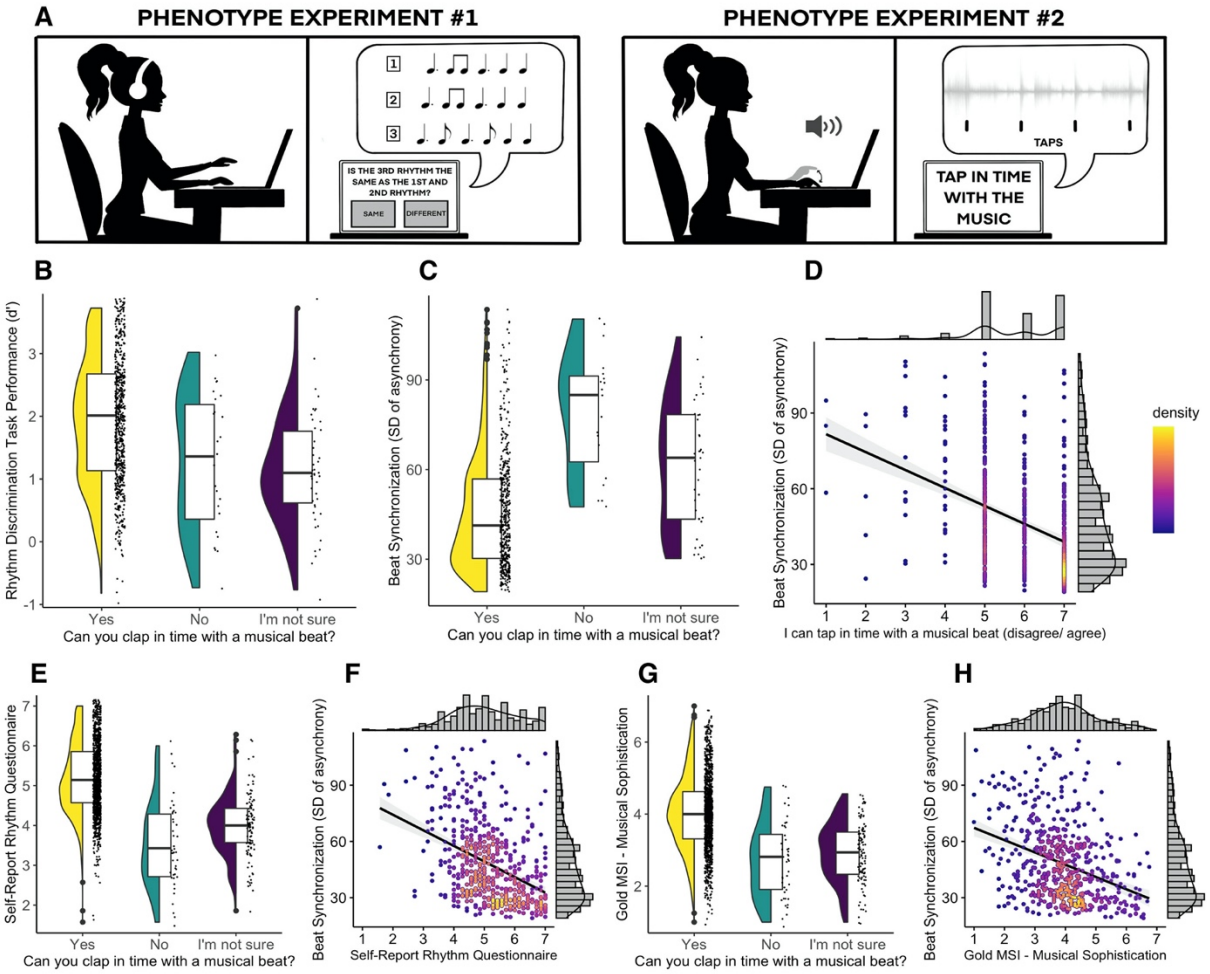

Figure 1. Phenotype validation studies overview and results. *A) Schema of internet-based phenotype validation studies.* In phenotype experiment #1, participants performed a musical rhythm perception test and provided self-report of the same target question in the GWAS study ("Can you clap in time with a musical beat"). In phenotype experiment #2, participants performed beat synchronization tasks (which involved tapping to the beat of musical excerpts) as well as responding to the same target question, in addition to a series of other questionnaires about their musical engagement/ability and health traits. B) Phenotype Experiment 1 results show rhythm perception task performance in association with responses to GWAS target question in N=724. C-H): Phenotype Experiment 2 results. C) Beat synchronization task performance in association with responses to the target question in n=542. D) Beat synchronization task performance in association with responses to a similar self-report question asked on a Likert scale, in n=542. E) Self-reported rhythm questionnaire (7-item scale) in association with responses to the target question in N=1,412. F) Beat synchronization task performance in association with Self-reported rhythm questionnaire in n=542. G) Gold-MSI (musical sophistication) in association with responses to the target question in N=1,412. H) Beat synchronization task performance in association with Gold-MSI in n=542.

Phenotype Experiment 1: Rhythm perception task performance.

Phenotype experiment #1 was conducted in N=724 participants recruited anonymously in Amazon's Mechanical Turk (see Table 1 for demographics).

Participants were asked the target question “Can you clap in time with a musical beat?” and performed a musical rhythm perception test (Supplementary Figure 1). See Methods and Supplementary Notes for experiment details. Briefly, in each of the 32 trials of the task, participants had to judge whether a pair of rhythms were the same or different (see Figure 1A), following a standard procedure for assessing individual differences in musical perception ability[31] and utilizing rhythm sequences with simple (highly metrical) and complex (syncopated) rhythms[50]. The rhythm perception task yielded quantitative scores.

Individuals with better performance in the rhythm perception test (higher total *d’*) were more likely to answer Yes to the target item (i.e. that they can clap to the beat: OR(95%CI)=1.94 [1.28 to 3.01], p=0.002, McFadden’s R^2=0.39), indicating there is approximately a 94% increase in the odds of answering ‘Yes’, per standard deviation increase in the rhythm perception test (see Figure 1B). In addition, individuals with higher scores on the subset of “simple” (i.e., more strongly beat-based) rhythm trials were more likely to answer that they can clap to the beat (OR(95%CI)=1.99[1.36-2.90], p<0.001, McFadden’s R^2=0.40.

Phenotype Experiment 2: Beat synchronization task performance

We conducted a second internet-based phenotype experiment (pre-registered in OSF) with N=1,412, to validate self-reported beat synchronization phenotype as a proxy for directly-measured beat synchronization ability (see Table 1 for demographics). Participants completed a questionnaire on musicality, health, and personality items, and were asked to tap in real time to the musical beat of 4 different musical excerpts (see

Supplementary Figure 2). Participants completed a questionnaire on musicality, health, and personality items, and were asked to tap in real time to the musical beat of 4 different musical excerpts (see Supplementary Figure 2). Beat synchronization tapping accuracy was assessed similarly to lab-based studies[32], but with a recently developed online-based technology that allowed us to precisely measure asynchrony of participants' taps along to music clips - i.e., REPP (Rhythm ExPeriment Platform; see[51]) for additional details on the experiment and pre-registered hypotheses (H1-H6), see Methods and Supplementary Notes. Key results of this study are summarized in Figure 1 and Supplementary Table 1. Note that better *tapping accuracy* is reflected in lower *tapping asynchrony* scores, i.e., more accurate timing of taps in relation to the beat.

First, we tested pre-registered H1, showing that individuals who respond Yes to the target question (i.e., "Can you clap in time with a musical beat") had lower tapping asynchrony, OR = 0.28, [0.18, 0.43], McFadden R^2 = .67 (Figure 1C). Tapping asynchrony was also negatively correlated with responses to a highly similar item ("I can tap in time to a musical beat") when asked on a seven-point Likert agreement scale (1= disagree; 7 = agree) instead of a "yes/no" answer, r = -.40, 95% CI [-0.47, -0.33] (H1a; Figure 1D). Similarly, individuals with significantly better self-reported rhythmic ability (based on responses to a seven-item questionnaire) were much more likely respond "yes" to the target question, OR = 7.34, 95% CI [4.79, 11.23], McFadden R^2=.34 (Figure 1E), and had lower tapping asynchrony, r = -.41, 95% CI [-0.47, -0.33] (Figure 1F) (H2). The results for H5 show that Musical sophistication scores from the Gold-MSI were also positively associated with the target question, OR=4.16, 95% CI [2.86, 6.04] (Figure 1G) and negatively correlated with tapping asynchrony r= -.34, 95%

237 CI [-0.42, -0.27] (Figure 1H). There was also no evidence that Musical Sophistication or
238 prior/current musician status (measured with an additional item) interacted with the
239 tapping asynchrony to predict responses to the target question (H6).

240 In addition, we demonstrated that although responses to the target question were
241 associated with confidence judgements of one's own tapping performance assessed
242 either immediately after the tapping trials, OR = 1.72, 95% CI [1.07, 2.76], or confidence
243 assessed as a personality trait, OR = 1.75, 95% CI [1.02, 3.00], controlling for these
244 confidence measures had no impact on the association with tapping asynchrony
245 described above, OR = 0.28, 95% CI [0.17, 0.44], McFadden R^2=.69 (H3). These
246 findings suggest that while the target question may encompass some self-reporting
247 bias, the bias does not diminish its strong association with true beat synchronization
248 ability. Moreover, all associations reported here were not altered when controlling for
249 age, sex, and education (see Supplementary Table 1).

250 **Genomic study population**

251 **Beat Synchronization GWAS sample**.

252 The study population for the discovery GWAS consisted of N=606,825 unrelated
253 participants of European ancestry (see Table 1 for demographics), who consented to
254 participate in research with 23andMe, Inc. and answered Yes or No to the target
255 question "Can you clap in time with a musical beat?" The majority of participants
256 answered 'Yes' (91.57%) and 8.43% answered 'No'. See Methods for further sample
257 details, genotyping, and quality control,.

258 **GWAS results and heritability estimation.**

GWAS was conducted using logistic regression under an additive genetic model, while adjusting for age, sex, the first five principal components from genetic data, and genotype platforms (see Methods). Sixty-eight "sentinel" SNPs (after two rounds of LD pruning, first at r^2=0.6 and then at r^2=0.1, kb = 250) at 67 genomic loci (locus 28 contains two independent sentinel SNPs) reached genome-wide significance ($p<5x10^{-8}$; Figure 2, Table 2, and Supplementary Table 2), with a total of 6,115 SNPs passing the genome-wide significance threshold. QQ-plot is provided in Supplementary Figure 3. Local association plots at each locus are provided in the Regional Plots supplemental document.

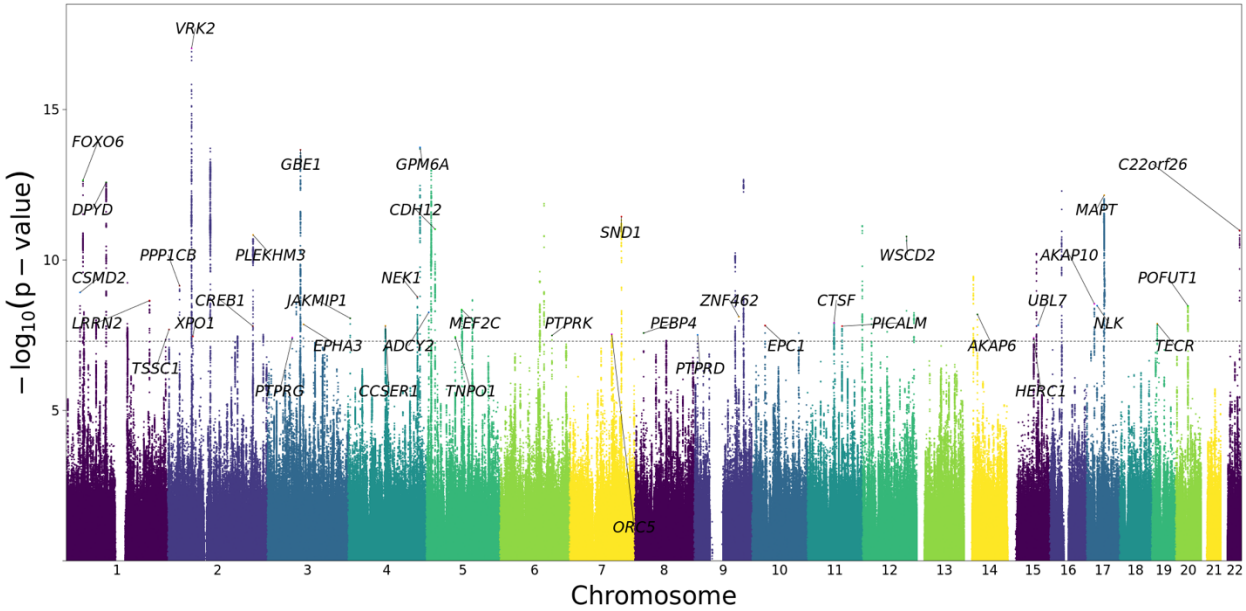

Figure 2. Manhattan plot of GWAS results of beat synchronization. Results are shown for 606,825 research participants with 23andMe who responded Yes (N=555,660) vs. No (N=51,165) to the question "Can you clap in time with a musical beat?", controlling for age, sex, top 5 PC's for ancestry, and genotype platform. The x-axis shows chromosomal position and the y-axis shows -log10 p-values). Sixty-seven loci (68 sentinel SNPs, with one locus containing two independent sentinel SNPs) surpassed the threshold for genome-wide significance of $p<5x10^{-8}$ (dotted horizontal line). For illustration purposes, only 500,000 SNPs with p<0.1 are shown; gene symbols for sentinel SNPs are notated when FUMA provided a gene mapped to nearest sentinel SNP.

278 The top associated locus was mapped at chromosome 2 close to *VRK2*
279 (Vaccinia Serine/Threonine Kinase 2) and *FANCL* genes (rs848293, $p=9.2 \times 10^{-18}$), a
280 region that has been linked to sleep, depression[52] and schizophrenia[53]. Another strongly
281 associated locus was around a SNP on chromosome 17 (rs4792891, $p=7.07 \times 10^{-13}$) that
282 maps to the Microtubule Associated Protein Tau (*MAPT*) gene, well-known for its
283 associations with Parkinson's disease[54]. There was also a locus on the Mitogen-
284 Activated Protein Kinase 3 (*MAPK3*) gene at 16p11.2, a region linked to risk for a
285 number of neurodevelopmental disorders including autism and schizophrenia[55], and to
286 verbal memory and language[56]. Another significantly associated gene was the
287 chromosome 4 Glycoprotein M6A (*GPM6A*), whose gene promoter contains a
288 transcription factor binding site for *GATA2*, a gene previously related to music
289 phenotypes[34].
290 Linkage Disequilibrium Score Regression (LDSC)[57] analyses revealed that
291 heritability estimates on the liability scale ranged from 13% to 16% when adjusted for a
292 range of estimated population prevalence of poor rhythm skills (from 3.0% to 6.5%;
293 Supplementary Table 3; see Supplementary Notes for explanation of prevalence
294 estimates). The observed (unadjusted) genetic variance explained 5% (se=0.0002) of
295 the phenotypic variance in the beat synchronization trait, with an LD score regression
296 intercept of 1.02 (se=0.01).
297
298 **Gene-based analyses.**
299 Gene-based association analyses performed with MAGMA v1.08 yielded 125
300 genes that surpassed the threshold of $p<2.6 \times 10^{-6}$ (Supplementary Table 4). The top two

301 genes are: *CCSER1,* in proximity to genes previously associated with musicality[58], and
302 *VRK2* (converging with the top locus identified in our SNP-based association analyses).
303 We also examined potential replication of genetic associations with musicality in
304 humans from prior reports (29 genes were selected: 26 reported in[58] plus *GATA2* and
305 *PCDH7*[34] and *UGT8*[59]). None of the genes reached statistical significance after
306 genome-wide correction ($p<2.6x\ 10^{-6}$; Supplementary Table 5, Supplementary Notes),
307 neither independently, nor as a gene-set (p=0.30), however, several are located near
308 *CCSER1* in the 4q22-24 region.

309 **Gene set enrichment analyses**

310 We performed gene-set enrichment analyses using MAGMA, implemented in
311 FUMA[60]. As hypothesized, associations with beat synchronization were significantly
312 enriched among genes expressed in brain tissue compared to those expressed in non-
313 brain tissues (Figure 3A); tissue-expression gene sets were based on GTEx data on 53
314 different tissue types[61]. To further examine potential biological pathways associated with
315 beat synchronization, we performed GO term and pathway enrichment analyses[62,63].
316 Three gene-sets out of 15,496 achieved statistical significance after Bonferroni
317 correction (Supplementary Table 6). Results were associated with nervous system
318 function, specifically: gene sets for synaptic membrane adhesion ($p=2.55\ x\ 10^{-8}$) and
319 synaptic adhesion-like molecules ($p=1.90x10^{-6}$), and MeCP2 regulation of transcription
320 factors ($p=1.17x10^{-6}$).
321

322 **Heritability Partitioning**

323 One advantage to SNP-based heritability estimation is the ability to partition
324 heritability according to genomic properties, which provides insight into the types of
325 genetic variation that contribute most to beat synchronization. To determine whether the
326 heritability of beat synchronization is enriched for specific functional categories,
327 stratified LDSC[64] was used to partition heritability (Supplementary Table 7). We
328 hypothesized that SNPs falling into open chromatin regulatory regions (i.e., accessible
329 to transcriptional machinery), and regions with human-specific variation, would be
330 enriched for beat synchronization-associated variation. When assessing broad SNP
331 annotation categories[65], we found enrichment in regions conserved in mammals
332 (regions of the genome identified under purifying selection[66]) (enrichment=15.8, p=1.19
333 x 10^{-12}) and in regulatory regions marked by acetylation of histone H3 at lysine 9
334 (H3K9ac; generally considered a marker for active chromatin; enrichment=8.0, p=1.85 x
335 10^{-8}) and monomethylation of histone H3 at lysine 4 (H3K4me1; generally considered a
336 marker for enhancers; enrichment=1.29, p=2.16 x 10^{-5}), supporting associations
337 mediated by effects on gene regulation.
338 Given the results of the broad categories showing enrichment in markers of
339 enhancers and active chromatin, we further used LDSC-Specifically Enriched Genes
340 (LDSC-SEG) heritability partitioning as described in[67] to examine whether genes
341 expressed in specific cell- or tissue-types (conditional to the other annotations) would
342 show enrichment for beat synchronization-associated variants. When assessing tissue-
343 specific annotations of active chromatin and enhancers (marked by H3K9ac, H3K27ac,
344 DNase hypersensitivity sites and H3K4me1), we found that heritability was enriched in
345 central-nervous-system- and skeletal muscle-specific regulatory regions; see

346 Supplementary Table 8 and Supplementary Figures 4, 5 and 6, for all cell-type specific,
347 multi-tissue chromatin, and multi-tissue gene expression results, respectively.
348 Enrichment in brain-specific regulatory elements, in several fetal and adult tissue-
349 specific elements as well as CNS-specific cell cultures, are shown in Figure 3B.
350
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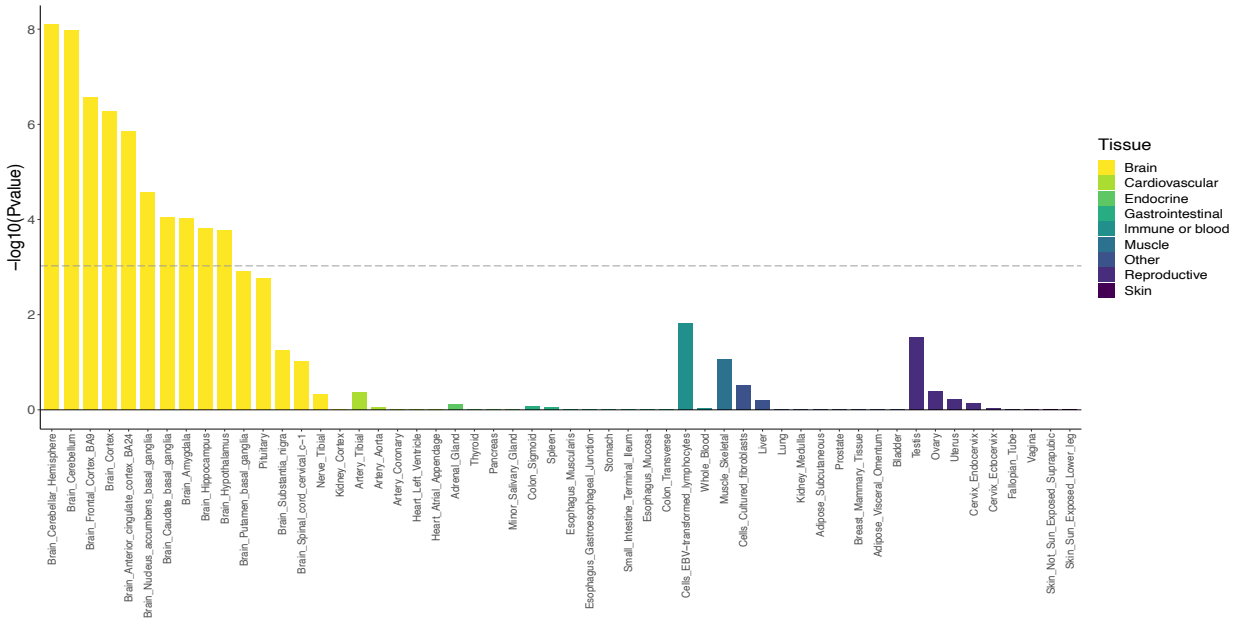

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353 **Figure 3A. Genes associated with beat synchronization are enriched for expression in brain tissue.** Results of
354 MAGMA gene-property analysis are based on gene expression levels from GTEx in 53 tissues. Associations with
355 beat synchronization were significantly enriched in brain-expressed genes (-log-10 p-values are on the y-axis, with
356 tissue type on the x-axis). Dotted line shows p-value threshold for significant enrichment after Bonferroni correction
357 for testing 53 tissues.
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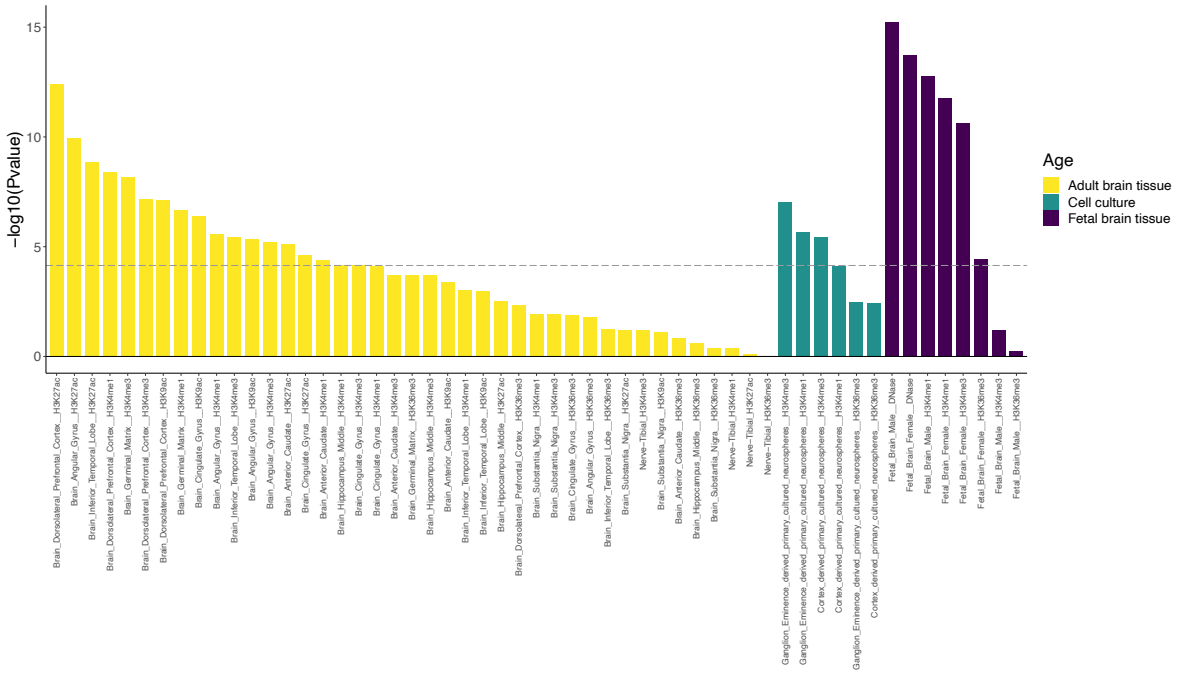

Figure 3B. Partitioned heritability shows enrichment in brain-specific regulatory regions of the genome. Partitioned heritability analysis was performed with LDSC-SEG. Tissue-specific regulatory elements are marked by histone 3 acetylation or DNase hypersensitivity (for open chromatin) and H3K4me1 (for enhancers). Regulatory regions in adult brain tissues are shown in yellow, with regulatory elements in in cell cultures in teal, and in fetal brain tissue shown in dark purple. The graph shows -log-10 p-values are on y-axis, with tissue and marker type on x-axis. The dotted line shows p-value threshold for significant enrichment after Bonferroni correction for number of gene sets tested.

Human Accelerated Region and Neanderthal Introgression Stratified Heritability Analyses

Given evolutionary hypotheses about the origins of rhythm[4,19,68], we evaluated the contribution of regions of the human genome that have experienced significant human-specific shifts in evolutionary pressure, using stratified LDSC[57,64]. In particular, we analyzed the contribution to beat synchronization heritability from variants in genomic loci that are conserved across non-human species, but have elevated substitution rate on the human lineage[69]. Many of these human accelerated regions (HARs) play roles in human-enriched traits[70], including cognition[71]. Two of the variants significantly ($p < 5x10^{-8}$) associated with beat synchronization (rs14316, rs1464791) fall

378 within HARs (occurring within our locus 66 and locus 20, respectively). This is 11.2
379 times more overlap than expected by chance (μ = 0.178 overlaps; p = 0.017, based on
380 10,000 permutations). The rs1464791 variant is near *GBE1*, a gene associated with
381 neuromuscular disease[72], reaction time[73] and cognitive deficits[74]. Applying LDSC to
382 consider the full set of association statistics, we find that genetic variants in HARs
383 contribute 2.26 times more to the observed heritability of beat synchronization than
384 would be expected if heritability were distributed uniformly across variants (p = 0.14).
385 Given the small number of common variants within HARs, this stratified heritability
386 analysis is substantially underpowered (0.17% of variants considered are in HARs). The
387 general agreement of these two approaches supports the enrichment of functional
388 variation relevant to beat synchronization in HARs.

389 We also evaluated the contribution of genetic variants detected in the
390 Neanderthal genome present in modern Eurasians due to interbreeding (hereafter
391 "Neanderthal variants") to the heritability of the beat synchronization phenotype.
392 Eurasian genomes contain ~1.5-4% of DNA as a result from interbreeding with
393 Neanderthals around 50,000 years ago. Heritability of beat synchronization was
394 significantly depleted among Neanderthal variants (1.97-fold depletion, p = 0.001).
395 However, Neanderthal ancestry is significantly depleted in functional genomic regions
396 overall[75]; therefore, the depletion of beat synchronization heritability in these regions is
397 likely the result of the overall depletion for Neanderthal ancestry in functional regions of
398 the genome. This is supported by a non-significant τ_c^*, illustrating that Neanderthal vs.
399 human variants do not provide unique heritability when conditioned on a broad set of
400 regulatory elements (Supplementary Table 9, Methods).

401

402 **Polygenic scores for beat synchronization are related to musicality reported in a**

403 **health care context**

404 We investigated whether the polygenic model of beat synchronization would be

405 associated with musicality, by examining whether a weighted sum of the common

406 alleles associated with beat synchronization, based on the GWAS results (also known

407 as polygenic scores [PGS]), differentiated musicians from non-musicians.

408 Musicians were drawn from recent study[76] that had algorithmically identified musically

409 active patients by the presence of specific musician-related keywords/regular

410 expressions in clinical documentation collected in the electronic health record (see

411 Methods and Supplementary Notes for details of automated search terms and chart

412 review validation details). Briefly, 1,753 musician cases (who also had linked genetic

413 data on file in the BioVU biobank) were compared with 65,147 genotyped controls. The

414 PGS for beat synchronization was significantly associated with musician status (OR per

415 SD increase in PGS, 1.26, 95%CI:1.20-1.33, $p<2 \times 10^{-16}$, Nagelkerke's R^2=1%)

416 (Supplementary Table 10, Figure 4), consistent with our hypothesis that the beat

417 synchronization phenotype captures a dimension of musicality. As expected, we did not

418 find evidence for associations of the beat synchronization PGS with the negative control

419 phenotypes (i.e., iron deficiency anemias, carcinoma in situ of skin, and cancer of the

420 brain).

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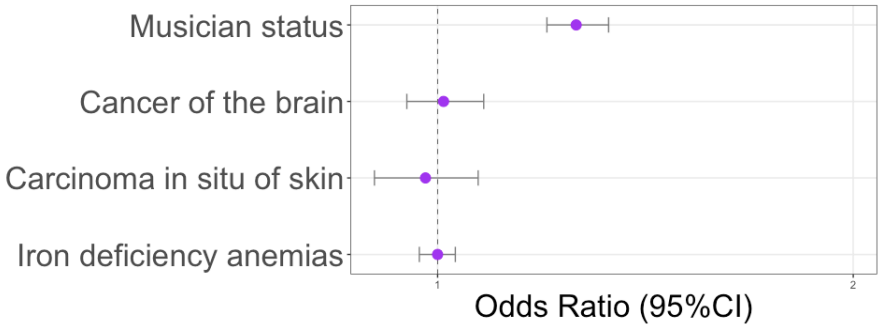

Figure 4. Polygenic score for beat synchronization predicts musicianship in electronic health record (EHR) biobank. With weights derived from the 23andMe beat synchronization GWAS, we applied polygenic scores (PGS) for beat synchronization to genomic data from N=1,753 musicians identified in Vanderbilt's BioVU compared to a control sample of N=65,147 (See Supplementary Notes). PGS-beat synchronization was associated with musician status (OR=1.26) but not with the three negative-control traits.

436 **Cross-trait analyses**

437 *Genetic correlations.* To determine if beat synchronization shares genetic
438 architecture with other traits, we tested genetic correlations[57] between beat
439 synchronization and all 764 available traits in LDHub (v.1.9.2) using LDscore
440 regression. This method is designed to show whether there is shared genetic variation
441 linked to a particular trait (here, our beat synchronization trait) and traits measured in
442 other GWAS studies. There were 31 statistically significant genetic correlations ($p<6.5 \times$
443 10^{-5}) between beat synchronization and other traits after adjusting for multiple
444 comparisons (Figure 5A, Supplementary Table 11). Briefly, top associations with beat
445 synchronization included grip strength (rg(left)=0.18, $p=3.6 \times 10^{-16}$, rg(right)=0.16,
446 $p=6.91 \times 10^{-15}$); peak expiratory flow from both the UKBiobank (rg=0.15, $p=2.11 \times 10^{-9}$)
447 and a second independent GWA study (rg=0.11, $p=6.6 \times 10^{-8}$), shortness of breath when
448 walking on level ground (rg = -0.16, $p=0.43 \times 10^{-5}$), and several other breathing/lung
449 function phenotypes (Supplementary Table 11). Processing speed measured as 'mean
450 time to correctly identify matches' was negatively genetically correlated with beat
451 synchronization ability (rg=-0.16, $p=3.22 \times 10^{-13}$) (i.e., faster processing speed was
452 associated with better beat synchronization). Additionally, smoking including 'ever
453 smoked' (rg=0.16, $p=2.5 \times 10^{-11}$) and 'past tobacco smoking' (rg=-0.15, $p=4.6 \times 10^{-10}$),
454 educational qualifications (O' levels/GCSEs or equivalent) (rg=0.16, $p=4.6 \times 10^{-7}$),
455 evening chronotype (rg=0.09, $p=3.8 \times 10^{-5}$) and tinnitus (rg=0.20, $p=6.7 \times 10^{-6}$) were all
456 positively associated with beat synchronization. While falling short of the correction for
457 multiple testing, exposure to loud music was also correlated with a similar point estimate

458 (rg=0.20, p=2.0 x 10^{-4}) and could be due to a relationship between tinnitus and loud
459 music exposure in the UKBB (r_g=0.30, p=4.8 x 10^{-6})[77,78].
460 *Genomic Structural Equation Modeling (SEM).* Next, we conducted Genomic
461 SEM[79] to examine whether the primary associations resulting from the exploratory
462 analyses represented distinct genetic correlations with beat synchronization and/or a
463 common set of genetic influences between beat synchronization and its top-associated
464 traits, some of which are also known to be related among each other in prior research
465 (e.g., musculoskeletal strength, lung function, and processing speed[80–82]). Analysis
466 details are reported in the Supplementary Notes. Briefly, we included the four most
467 significant traits from the LDHub analyses (grip strength, processing speed, smoking,
468 lung function), creating latent factors where possible using other GWAS from these
469 categories that were also significant in LDHub analyses (e.g., “Ever smoked”, “Smoking
470 status: Previous”, “Light smokers: At least 100 smokes in lifetime”). The final model,
471 displayed in Figure 5B, suggested that associations between beat synchronization,
472 reaction time, grip strength, and lung function were explained by a common set of
473 genetic influences, accounting for 16% of the total variance in the beat synchronization
474 GWAS (the squared factor loading of 0.40 on the Common factor). Beat synchronization
475 was genetically associated with smoking through a separate genetic association
476 (r=0.16; 95% CI [0.10, 0.23]), as smoking was uncorrelated with the other factors (see
477 Supplementary Notes for more information).
478

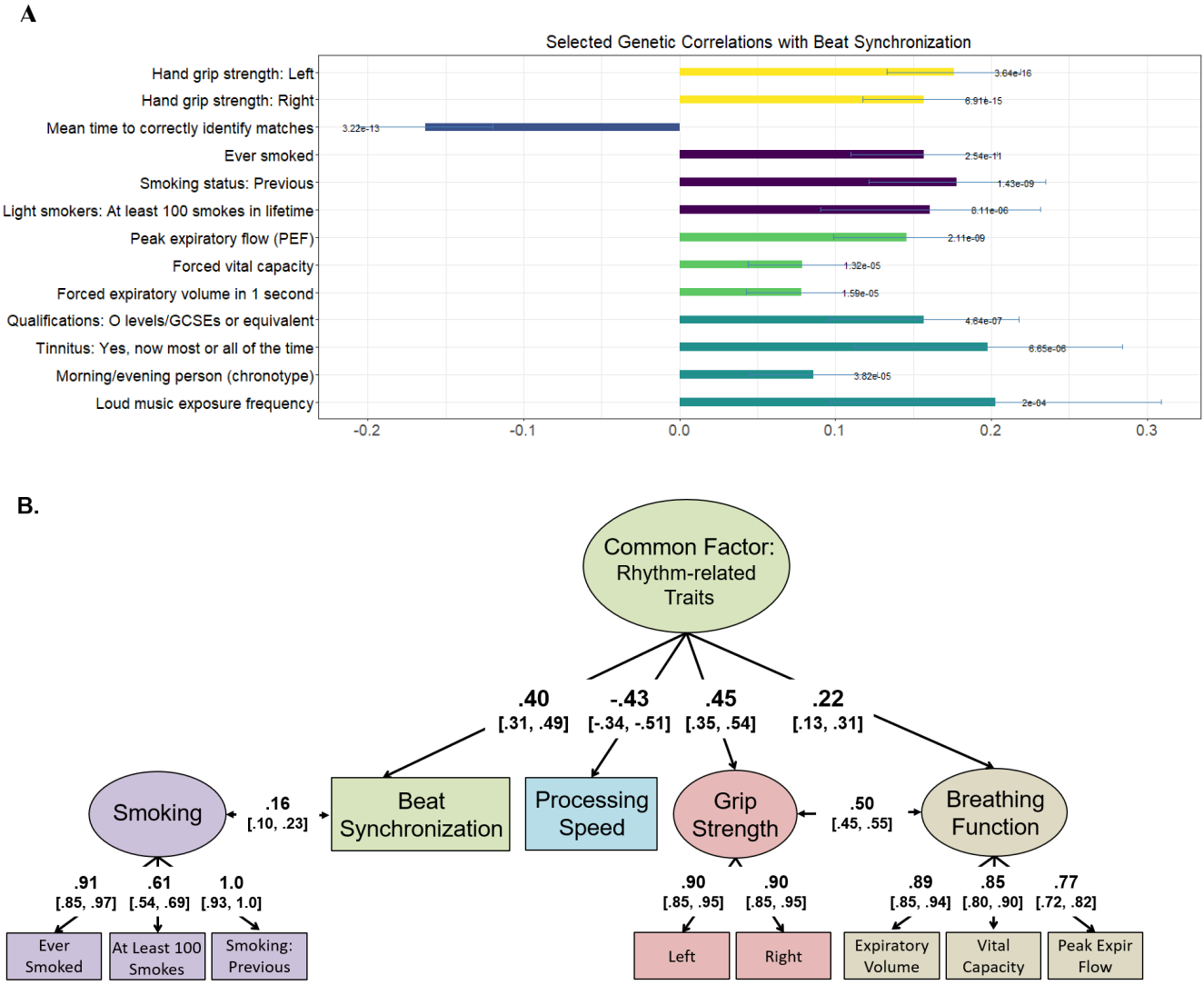

Figure 5. Selected results from the cross-trait genetic correlations analysis. Beat synchronization summary statistics were significantly genetically correlated with several health, cognitive, emotion, and circadian phenotypes in our analysis comparing beat synchronization to traits available in LDHub. **(A)** The most significant genetic associations from exploratory analyses of LDHub traits, along with other selected traits. The y-axis is the rg correlation, the bars represent standard errors and the p-values are also indicated. Full results are presented in Supplementary Table 11. **(B)** The best-fitting genomic structure equation model of beat synchronization with GWAS of grip strength, breathing, smoking, and processing speed from LDHub. 95% confidence intervals of factor loadings and correlations are displayed in brackets. Results suggest that beat synchronization was associated with the other traits (except smoking) through a set of common genetic influences. Model fit: χ^2 (31) = 7136.92, p < .001, CFI = .982, SRMR = .041.

Common Factor GWAS: Rhythm-Related Traits. Using genomic SEM, we conducted a multivariate GWAS on the latent genetic factor from the Common variance in the model presented above and portrayed in Figure 5B, after excluding smoking from

498 the model and restricting to one set of summary statistics per domain (beat
499 synchronization, processing speed, peak expiratory flow, grip strength [left]). The
500 heritability of this latent genetic factor was .1068 (s.e.=0.0038). There were 270
501 independent genome-wide significant sentinel SNPs, 97 lead SNPs, and 80 genomic
502 risk loci (Supplementary Table 12). Heritability was enriched for genes expressed in
503 cerebellum. See Supplementary Figures 7 and 8 for the Manhattan plot and tissue
504 expression plots, and Supplementary Notes for more detail.
505
506 **Sensitivity analyses.**
507 We conducted sensitivity analyses to examine whether 1) the GWAS beat
508 synchronization results are due to shared genetic effects with cognitive ability; 2) the
509 GWAS genetic correlation results are driven by subtle residual population substructure;
510 3) the inversion on chromosome 17q21 is associated with local ancestry in our study
511 sample; and 4) the MAPT association is due to the presence of patients with
512 Parkinson's in the sample. These analyses demonstrated that our results are robust to
513 each of these potential biases (Supplementary Notes).
514
515 **Cross-trait phenotypic extension of genetic correlations.**
516 Data from Phenotype Experiment 2 was analyzed to examine whether the
517 genetic associations between beat synchronization we uncovered from LDSC
518 regression would be reflected in true phenotypic associations (H4 of the pre-
519 registration). Poor tapping accuracy was weakly associated with a morningness
520 preference (r=-.10), more shortness of breath (r=-.16), and smoking 20 or more

521 (lifetime) cigarettes (r=-.11) (Supplementary Table 13). Association with tinnitus and
522 loud music exposure were nonsignificant. In other words, individuals who had better
523 beat synchronization task performance were more likely to report eveningness
524 chronotype, less likely to report shortness of breath when walking on level ground
525 (these associations go in the same direction of the genetic study). However, they were
526 less likely to report ever smoking, and less likely to report tinnitus (these associations
527 were opposite of what was found in the genetic study). The association with loud music
528 exposure was nonsignificant. These associations with chronotype, shortness of breath,
529 and smoking remained significant after controlling for age, sex and education, and/or
530 removing professional musicians from the sample. Self-reported rhythm (assessed
531 using the seven-item Rhythm scale) was only associated with smoking status (r=-.08)
532 and loud music exposure (r=-.13), even when controlling for covariates or focusing on
533 non-musicians; however, these associations appeared in the opposite direction of the
534 corresponding genetic associations. There was no evidence of interactions with musical
535 sophistication or prior/current musician status for the H4 constructs, except that the
536 association between loud music exposure and self-reported rhythm was weaker in
537 individuals with who more actively performed music (p=.022), though this effect would
538 not survive a strict multiple test correction.

539 **Discussion**

540 This study demonstrates that common genetic variation plays a role in
541 synchronizing to a musical beat, complementing prior evidence of innate human rhythm
542 sensitivity[4,19]. We conducted a GWAS of beat synchronization in more than half a million
543 individuals surveyed within 23andMe, Inc., with the resulting summary statistics and
544 post-GWAS analyses representing a significant advancement of our understanding of
545 the genomic basis of a musicality phenotype. Heritability of beat synchronization is
546 enriched for functions of the central nervous system on a number of dimensions (gene
547 expression in brain tissue, genes involved in synaptic function, and more generally,
548 genes involved in neural development and brain-specific regulatory regions of the
549 genome). We successfully applied polygenic scores for beat synchronization to a
550 separate cohort to predict musicianship, showing that the GWAS taps into the larger
551 construct of musicality. Our findings point to pleiotropy between beat synchronization
552 and several other types of biological functions (breathing function, motor function,
553 processing speed, and chronotype), paving the way to a better understanding of the
554 biological underpinnings of musicality and its health relevance.

555 Of course, the interpretation of these results depends upon a valid phenotype. In
556 a series of phenotypic experiments, we demonstrate that self-reported beat
557 synchronization/rhythm measures can be used in large-scale population-based studies
558 as suitable proxies for measuring individual differences in beat synchronization ability.
559 Our findings indicate that the “target question” phenotype used in the genetic study
560 (*Can you clap in time with a musical beat?*) was highly related to beat synchronization
561 task performance (i.e., accuracy in tapping along to musical excerpts). We show that

562 the GWAS phenotype is also significantly associated with the following: rhythm
563 perception task performance[50], a self-report Rhythm scale (generated from an additional
564 questionnaire), and a well-established assessment of musical sophistication[48]. These
565 results also converge with findings from prior work in small samples that show shared
566 variance among task performance of beat synchronization, rhythm perception, and
567 musical engagement/training[49,83–86]. The phenotypic associations were robust to
568 demographic factors (age, sex, level of education) and confidence (both as a
569 personality trait and as confidence in assessing one's own tapping accuracy), and were
570 not driven by the presence of professional musicians in the sample. More generally, our
571 findings indicate that people were able to self-report their rhythm abilities accurately
572 using other similar questionnaire items (i.e., scale from a seven-item Rhythm
573 questionnaire and a Likert scale single item both predict tapping accuracy). These
574 phenotype validation studies represent critical groundwork enabling self-reported
575 rhythm traits to be deployed online in large-scale population genetic cohorts where
576 participant assessment time and technology are constrained.
577 Beat synchronization exhibited a highly polygenic architecture, with sixty-seven
578 loci surpassing the threshold for genome-wide significance. The top-associated locus
579 (at sentinel SNP rs848293) mapped to *VRK2*, a protein kinase with multiple spliced
580 isoforms expressed in the brain that was previously associated with behavioral and
581 psychiatric phenotypes (i.e. depression[52], schizophrenia[53] and developmental delay[87]),
582 suggesting a biological connection between rhythm and neurodevelopment. The SNP-
583 based heritability of beat synchronization on the liability scale was moderate, ranging
584 from 13 to 16%, similar to heritability estimates of other complex traits (e.g., chronotype

585 GWAS[88]) and consistent with moderate heritability estimates of musical rhythm abilities
586 reported in twin studies[35–37].
587 We used complementary methods (tissue-specific GTex-based gene set
588 enrichment analysis in MAGMA, and partitioned heritability in tissue-specific expressed
589 genes and regulatory regions with LDSC-SEG) to examine potential mechanisms linking
590 genetic variation to neural architecture of the beat synchronization trait. Collectively,
591 results showed enrichment of the heritability of beat synchronization in many brain
592 tissues including cerebellum, dorso-lateral prefrontal cortex, inferior temporal lobe, and
593 several basal ganglia nuclei (including putamen, caudate, and nucleus accumbens).
594 This pattern of results likely reflects a genetic contribution to subcortical-cortical
595 networks underlying musical rhythm perception and production[28]. It is important to note
596 that because of the highly overlapping gene expression and chromatin signatures
597 between related tissues, with differences reflecting both function and cell type
598 composition, these results do not yet allow us to directly compare the respective
599 contributions different enriched brain regions. Rather, enrichment of brain-tissue-
600 specific enhancers and active-regulatory regions, and enrichment of expression in brain
601 tissue, suggest that regions of the genome involved in regulation of gene expression
602 play a role in the beat synchronization trait. Moreover, partitioning heritability chromatin
603 results showed an enrichment in both fetal and adult brain tissues, suggesting that beat
604 synchronization may be the result of neurodevelopmental or basic brain processes.
605 Gene set enrichments were also observed for synaptic function and MeCP2
606 transcription regulation in the nervous system. Taken together, these results are a
607 building block towards understanding how genes influence neural processes during

608 beat perception and production, complementing results obtained with neuroimaging
609 methods[89–94].
610 Insights about the evolution of rhythm traits are suggested by the occurrence of
611 two of the beat-synchronization-associated loci in human-accelerated regions (HARS)
612 of the genome. In particular, rs1464791 is an expressive quantitative trait locus (eQTL)
613 that regulates expression of *GBE1* in multiple tissues, including adrenal gland and
614 muscle[61]; *GBE1* is also linked to neuromuscular disease[72] and reaction time[73]. HARs
615 are involved in many functions, so it is difficult to explicitly link their accelerated
616 evolution to beat synchronization. It is too early to tell whether the overlap between beat
617 synchronization-associated loci and those two HARS supports evolutionary theories
618 about music (e.g., groups moving to a beat in synchrony during joint music-making
619 and/or temporal coordination of movement between parents and young children have
620 been posited to exert selective pressures in early humans by enhancing group social
621 cohesion and family bonding[27,95]). The contribution of the genetic architecture of
622 musculo-skeletal systems and motor function to beat synchronization is further
623 suggested by enriched heritability of SNPs that are enhancers located in
624 musculoskeletal-tissue-specific regulatory regions of the genome, as well as our
625 findings of genetic correlations between grip strength and beat synchronization.
626 We derived polygenic scores (PGS) generated from the beat synchronization
627 GWAS to a separate genetically informative sample (in a healthcare biobank),
628 demonstrating that beat synchronization PGS's are significantly associated with
629 musicianship. These findings suggest that the genetic signature of musical beat
630 synchronization is more widely tied to the biology of musicality, a finding corroborated in

631 Phenotype Experiment 2 by phenotypic associations between musical engagement,
632 measured beat synchronization (tapping accuracy), and self-reported rhythm ability.
633 These results also align with literature on other related biological bases of musicality
634 and rhythm, i.e., brain network activity during rhythmic tasks and the effects of plasticity-
635 related effects of musical expertise[28].

636 Moreover, our findings are promising for future large-scale genomic
637 interrogations using comprehensive music phenotyping yielding continuous musicality
638 variables (whether questionnaire-based[48,96] or measured aptitude-based variables[35]).
639 When this new field examines GWAS results on other heritable musicality traits such as
640 pitch discrimination and music training, future work can examine potential genetic
641 correlations between beat synchronization and other musical traits as predicted by
642 family-based studies[33,34,38,97]. While the current data show a clear connection between
643 the beat synchronization and broader musicality at the phenotypic and genetic levels,
644 further genomic investigation in well-powered samples is needed to disentangle the
645 *specificity* of genetic influences on rhythm from more general genetic influences on
646 musical ability.

647 The ability to move in synchrony to a musical beat encompasses beat perception
648 and extraction, motor periodicity, meter perception, and auditory-motor entrainment (see
649 Glossary in Supplementary Notes and[4,28,98]). Despite this complexity, beat is a highly
650 frequent feature of many musical systems[1,3,27]. For Western participants, beat
651 perception and production does not depend on musical training or a particular genre of
652 music (note that deficits in beat synchronization are not linked to lack of music
653 exposure[99]). A limitation of the current work is the restriction of the genetic sample to a

654 European ancestry (due to GWAS methodology constraints); investigating beat
655 synchronization, musicality, and cross-trait correlations in populations of non-European
656 ancestry should be a future priority for capturing the spectra of musicality in a wider
657 range of ethnic, cultural and socio-economic contexts (see[100]). It is important to note
658 that early research on individual differences in music ability in the early 1900's was
659 pursued not only using what we now recognize as highly culturally biased assessments,
660 but also explicitly through the lens of eugenics (see[101]), similar to early research on
661 individual differences in cognition. We strongly condemn the design and intent of those
662 studies, and emphasize that even a robust polygenic model for beat synchronization (or
663 musicality in general) cannot make deterministic predictions about a specific individual's
664 actual ability; rather, these models are probabilistic at the group level[102], and explain
665 only a small part of the etiology of complex traits[103]. Furthermore, new knowledge on
666 the genetic basis of musicality must be used ethically and fairly for research discovery
667 and never for harm (e.g., preventing children's access to musical activities).
668 We replicated previous findings implicating location 4q22.1 in musicality-related
669 traits[33,59] (*CCSER1* was the top-associated gene in our MAGMA analysis), but did not
670 find support for previous gene associations from a set of genes that was drawn from
671 prior candidate-gene, linkage, and GWAS studies with relatively small samples[58]. This is
672 potentially due to well-known methodological problems with these methods particularly
673 when applied to complex traits in small samples[104]. Without a second comparably sized
674 GWAS available within which to conduct replication of the loci discovered in the primary
675 GWAS, we were still able to demonstrate generalizability of these results by showing
676 that PGS for beat synchronization predicts a musical trait in a separate biobank sample.

677 The genetic architecture of beat synchronization also remained virtually unchanged
678 after conditioning the analyses on known GWAS markers of intelligence, in line with twin
679 studies showing specific genetic effects of rhythmic aptitude, over and above any
680 common genetic influences on rhythm and intelligence[36,105].

681 Our multi-pronged genetic cross-trait explorations revealed pleiotropic effects
682 between beat synchronization and several traits, including types of biological rhythms
683 (breathing-related phenotypes and circadian chronotypes); these were verified by
684 phenotypic replication of selected associations in an additional experiment. We initially
685 discovered novel genetic correlations between beat synchronization and specific health
686 and cognitive traits (i.e., increased breathing function, greater grip strength, and faster
687 processing speed) consistent with prior phenotypic and behavioral genetic studies of
688 cognition, sensory processing, and musicality[97,106–108]. We further explored these novel
689 associations with genomic SEM, which revealed common genetic variance among beat
690 synchronization and breathing function, musculoskeletal function, and cognitive function
691 (with the latter three traits previously shown to be genetically interrelated during the
692 aging process[80,81]). Poor beat synchronization could be tied to certain health risks
693 during aging, in light of other genetic and epidemiological work showing that lung
694 function decline predicts later declines in motor function and psychomotor speed in
695 older adults[109–112]. We replicated the positive genetic correlation between better beat
696 synchronization ability (accuracy in tapping to the beat of musical excerpts) and lung
697 capacity in our phenotype validation study, where we also found that better beat
698 synchronization task performance was related to lower likelihood of shortness of breath.

699 Thus, the LDSC and genomic SEM results suggest that beat synchronization
700 shares common biology with a constellation of related health traits, converging with the
701 growing literature on the overlapping biomechanical and perceptual mechanisms of
702 rhythms harnessed during synchronization, communication, muscle tensioning, and
703 breathing. The cerebellum in particular governs certain neural mechanisms shared
704 among these processes and plays important roles in the control of coordinated
705 movement, balance, respiration, dance, and even rhythm perception during passive
706 listening to music[29]. The rhythm-related traits multi-variate GWAS obtained with
707 Genomic SEM resulted in 80 genome-wide significant loci and enriched heritability of
708 genes expressed in Cerebellar tissue. Such phenomenon reflecting potentially shared
709 biology across a broad range of physiological and developmental processes has been
710 the focus of recent frameworks in which the ontogeny of rhythm, and more specifically
711 of sensitivity to beat synchronization, are been hypothesized to play a role very early in
712 life in its potential connections with maternal breathing and locomotion[113]. Experiments
713 in infants demonstrate that parental singing and rocking help to regulate newborn
714 breathing[114] and that infants reap the socio-emotional benefits of their caregivers' beat-
715 synchronous interactions even before they possess the motor coordination to
716 synchronize precisely to music[115]. Respiratory and upper limb movements have been
717 found to be functionally synchronized during vocalization such that listeners can detect
718 nuances of oscillatory body movement in an unseen speaker's vocalizations even when
719 highly constrained[5]. "Beat gestures" in speech involve the cerebellum[116] and are
720 inextricably linked to respiration, upper limb movement, and postural control, all of which
721 may be biomechanically related to tapping or clapping to music.

722 In addition, we identified a new relationship between chronotype and beat
723 synchronization (genetic correlation between eveningness and beat synchronization
724 GWAS) and replicated this phenotypically in our pre-registered Phenotype Experiment
725 in which we found that individuals who self-identified as 'evening people' tended to tap
726 more accurately to music. This particular association was not moderated by musical
727 sophistication scores, and survived sensitivity analysis in which professional musicians
728 were removed. These results complement recent evidence of the increased prevalence
729 of eveningness in musicians[117], indicating that the relationship between chronotype and
730 musicianship cannot solely be explained by environment (i.e., nocturnal job demands of
731 professional musicians), but that also other shared biological factors may play a role.
732 Our case/control GWAS has allowed us to effectively identify genetic alleles
733 differentially associated with normative beat synchronization vs. beat impairment,
734 complementing neural evidence of beat synchronization networks[83,85,86,99]. Future
735 genetic studies could also examine beat synchronization task performance as a
736 continuous trait, either through self-report or online-based methods directly measuring
737 participants' tapping accuracy, such as demonstrated in Phenotype Experiment 2 using
738 REPP[51]. Prior literature on liability threshold models has shown that case-control GWAS
739 of complex traits yield similar results to those obtained through continuous phenotypic
740 measures (for example, the genetic architecture of continuous measures of psychiatric
741 symptoms is highly similar to the genetic architecture of cases versus controls[118]).
742 Finally, although our GWAS was based on self-report, previous studies of other health
743 traits based on self-report have effectively replicated associations from studies using

744 validated assessments, indicating that a powerful sample size can overcome limitations
745 arising from phenotyping error[119].
746 Taken together, our results advance knowledge of the biological basis of beat
747 synchronization by identifying genomic regions associated with individual differences in
748 beat synchronization, estimating its cumulative SNP-based heritability, successfully
749 applying a polygenic score model in a separate genetic sample, and exploring the
750 enrichment of heritability in genes tied to central nervous system function. Movement in
751 synchrony with a musical beat is a fundamental feature of music, and sensitivity to the
752 beat emerges early in development, supporting childhood development in numerous
753 ways[3,11,40,43] and with importance over the lifespan[120]. By elucidating the genetic
754 architecture of beat synchronization, we were able to identify the source of some of the
755 phenotypic variation observed in the general population and reveal health relevance
756 through cross-trait analyses. This study also provides a solid foundation for future
757 exploration of how specific genetic variants contribute to neural mechanisms of
758 entrainment, prediction, and reward harnessed during musical interactions.

759 **Methods**

760 **Phenotype validation studies**

761 ***Phenotype Validation Experiment 1.***

762 *Overview.*

763 Phenotype Validation Experiment 1 was designed to determine if self-reported rhythm
764 abilities measured with the question used in the GWAS (i.e., 'Can you clap in time with
765 a musical beat?') would be associated with task-based rhythm perception performance.
766 The study was conducted in Amazon's Mechanical Turk and received ethical approval
767 from the Columbia University Institutional Review Board; participants gave their written
768 informed consent. We selected the Beat-based Advantage paradigm as a rhythm
769 discrimination (perception) test due to its design of stimuli with simple and complex
770 meter[121] and prior history investigating individual differences in rhythm perception in a
771 variety of brain and behavioural studies in adults and children with typical and atypical
772 development[30,50,122,123] as well as feasibility for internet-based adaptation. A
773 questionnaire (self-report questions) was administered prior to the perception task, to
774 avoid biasing participant self-report responses by how they perceived their own task
775 performance. See Supplementary Notes for additional details on procedure and self-
776 report questionnaire.

777

778 *Participants*

779 The study sample was N=724 individuals who consented and passed a common
780 headphone check[124] that guarantees good listening conditions and the ability to follow
781 basic instructions; this test also effectively filters out bots. Participants (333 females;

387 males; 4 “other”) were 18-73 years old (mean = 36.1 years, SD=10.9) with 0-45 years of self-reported musical experience (mean 3.7 years, SD=5.8), representing an average degree of musical experience (see norms in[48]); demographics are reported in Table 1 (note that n=2 did not report their age).

Rhythm Perception Task

Stimuli for the rhythm perception task consisted of 32 rhythms drawn from prior work[50,121]. For each participant, we randomized with probability of one half the occurrence of “simple” rhythms (strong beat-based metrical structure and generally easier to discriminate) and “complex” rhythms (weaker metrical structure due to syncopation and generally more challenging to discriminate). Each rhythm was presented using pure tone stimuli in one of 6 frequencies (294, 353, 411, 470, 528, and 587 Hz, selected at random), and one of 4 durations (ISI of 220, 230, 240, and 250 ms). Each trial consisted of 3 rhythms separated by 1500 ms of silence. The two first presentations were always identical, and in half of the trials (counterbalanced) the third rhythm was also identical (standard condition); in the other half of the trials, the rhythm differed by having one interval swapped (deviant condition). The pairings and structure of standard and deviant trials were taken from[50]. Participants were instructed that in each trial, they would listen to the series of three rhythms (the first two were always identical, and the third could be the same or different), and they had to indicate if the third rhythm was the same or different (see Supplementary Figure 1). Additional technical details are provided in the Supplementary Notes.

Data analysis.

Self-report. Responses to the target question 'Can you clap in time with a musical beat?' were as follows: n=654 (90.3%) participants answered 'Yes', n=25 (3.5%) answered 'No' and n=45 (6.2%) answered "I'm not sure." Regarding an additional self-report question 'Do you have a good sense of rhythm?', n=503(67%) answered 'Yes', 102(14%) answered 'No' and n=117(16%) answered 'I don't know'. n=488 answered 'Yes' to both questions; the tetrachoric correlation between these two self-report questions was r=0.73.

Rhythm perception test. Responses to the rhythm perception test were analysed using signal detection theory[50,125]; this method is appropriate for discrimination tasks where the participant has to categorize stimuli along some dimension with the resulting *d'* values the strength of detection of the signal relative to noise. *d'* values were calculated on the 32 test trials. As expected from prior work[50,126], individuals performed better at discriminating simple rhythms (mean d'= 1.98, SD =0.91) than complex rhythms (mean d'=1.43, SD =0.97) ($t(724)=11.11$, $p<2.2 \times 10^{-16}$, Cohen's d=0.58).

To examine whether the target question was related to the objective performance on the rhythm perception test, we performed a logistic regression analysis in which the clap-beat target question (Yes vs. No) was the outcome and quantitative scores on the rhythm perception test performance (standardized *d'* scores mean = 0, SD = 1) were the predictor. Covariates included age, education, and sex. McFadden's R^2 was also computed. We did not include 'I'm not sure' in the regressions, because this response was not available for data analysis in the GWAS. Given that the simple rhythms have a strong metrical structure that is known to facilitate detection and synchronization of the

beat[50], we also tested whether performance on the simple rhythm trials predicted self-reported beat synchronization (i.e., those who responded Yes to the clap-beat question).

Phenotype Experiment 2.

Overview.

The aims of Phenotype Experiment 2 were two-fold: 1) to validate self-reported beat synchronization phenotype as a proxy for objectively measured beat synchronization ability, and 2) to explore phenotypic associations between rhythm/beat synchronization and assorted traits found to be genetically correlated with beat synchronization. Phenotype Experiment 2 was pre-registered in OSF prior to data collection. This internet-based study consisted of a beat synchronization task to assess the accuracy of participants' tapping in time with musical excerpts, and a series of questionnaires assessing self-reported rhythm, musicality/music engagement, selected health traits, confidence as a personality trait, and demographics. We used REPP[51] to measure participants' tapping responses online with high temporal fidelity. The item from the GWAS study, "Can you clap in time with a musical beat?" with possible responses: Yes/No/I'm not sure, is referred to as the "target question."

We tested the following hypotheses: *H1*: Self-report responses to the target question will be correlated with beat synchronization task performance (i.e., accuracy of tapping to the beat of music), such that individuals who respond Yes to the "target question" are predicted to tap more accurately to the beat of musical excerpts (i.e., they will have lower standard deviation of asynchrony than individuals who respond No to the

target question). *H1*a: Self-report on a highly similar self-report question ("I can tap in time with a musical beat") with responses on a 7-point agreement Likert scale are predicted to be correlated with tapping accuracy. *H2a:* The target question will be associated with broader rhythm ability/engagement (measured with a rhythm scale from other self-report questions). *H2b:* Beat synchronization task performance reflects broader self-reported rhythm ability/engagement. *H3:* To examine whether confidence (either as a personality trait or sureness in one's own task performance) affects the reliability of self-reported beat synchronization. *H4:* Selected traits found to be genetically correlated with beat synchronization in the GWAS will be phenotypically correlated with beat synchronization task performance and the Rhythm Scale. Specifically: better beat/rhythm is correlated with evening chronotype (H4a), less shortness of breath (H4b), more tinnitus and loud music exposure (H4c), and more smoking (H4d); and that these associations would survive controlling for age, sex, and education (H4e). *H5.* Responses to the target question will be positively correlated with musical engagement measured with the Gold-MSI. *H6*. The associations in H4 would interact with being a musician, or more generally, with musical engagement.

Participants.

A total of N=1,412 individuals met participation criteria outlined in the pre-registration (including passing the attention check item and not abandoning the study before completion). The study took place in Amazon Mechanical Turk and all participants provided informed consent in accordance with the Max Planck Society Ethics Council's approved protocol. Participants (728 females; 678 males; 6 prefer not

answer) were 18-77 years old (mean=36.3 years, SD=11.9) and had of 1-2 years of self-reported musical experience. To ensure that the tapping technology measured beat synchronization with high temporal fidelity, it was crucial that participants complied with instructions to perform the tapping task (e.g., using the laptop speakers instead of headphones, with minimal background noise, etc.), and also used hardware and software without any technical issues that would preclude the recording signal (e.g., malfunctioning speakers or microphones, or the use of strong noise cancellation technology; see[51]). Thus, several precautions, including calibration tests and practice trials, were taken to make sure the tapping technology would work effectively, excluding cases that did not meet the requirements (see Supplementary materials for details). A subset of n=542 had appropriate hardware to complete all parts of the study (including the tapping tests). Questionnaires were administered in the full sample of participants. Sample demographics are reported in Table 1. Demographics of the participants that completed the tapping experiment was highly similar to the full sample, as shown in the table; furthermore, 65.3% of the full sample and 64.9% of tapping sample had a Bachelor's degree or higher.

Data collection for Phenotype Experiment 2.

The first questionnaire included self-report items, including the "target question," and also covering a variety of musical, health, and interest phenotypes. The health phenotype questions were chosen from phenotypes (chronotype, smoking, shortness of breath, tinnitus, and loud music exposure) found to be genetically correlated with beat synchronization in our genetic analyses. Rhythm questions were selected for their

897 particular relevance to various aspects of interacting/engaging with musical rhythm. The
898 order of the questions was fixed for all participants. In addition, we used an attention
899 check item[127] between item 10 and 11, in order to exclude fraudulent responders, such
900 as computer bots or disengaged participants responding randomly to the experiments.
901 The end-questionnaire consisted of items covering the following additional self-report
902 topics: another question about being a musician, a task confidence rating question, a
903 Confidence scale, a 16-item short version of the Gold-MSI[48] (items were chosen due to
904 their high reliability scores: reliability omega = 0.92), and a Demographic questionnaire.
905 Questionnaire items for Phenotype Experiment 2 are listed in the Appendix of the
906 Supplementary Notes.

907 *Tapping technology.* Beat synchronization is particularly challenging to study with
908 online research, where variability in participants' hardware and software can introduce
909 all kinds of delay in latency and jitter into the recorded time stamps[128,129]. Here we used
910 REPP (see[51] for full details and a validation study of the technology), a robust cross-
911 platform solution for measuring sensorimotor synchronization in online experiments that
912 has high temporal fidelity and can work efficiently using hardware and software
913 available to most participants online. To address core issues related to latency and
914 jitter, REPP uses a free-field recording approach: specifically, the audio stimulus is
915 played through the laptop speakers and the original signal is simultaneously recorded
916 with participants' tapping responses using the built-in microphone. The resulting
917 recording is then analyzed using signal processing techniques to extract and align
918 timing cues with high temporal accuracy.

Beat synchronization task. The beat synchronization task procedure consisted of three parts: calibration tests, practice phase, and main tapping phase. Participants started with the calibration tests, including a volume test to calibrate the volume of the laptop speakers to a level sufficient for detection by the microphone, a background noise test to make sure participants were in a quiet environment, and a tapping test to help participants practice how to tap on the surface of their laptop in the right level and location to be detected by the microphone. Participants were then presented with the practice phase, which consisted of four 15-second trials of isochronous tapping to a metronome beat (two with inter-onset interval of 500 msec and two with inter-onset interval of 600 msec). Following the practice phase, participants were presented with the main tapping task consisting of eight trials (4 musical excerpts, each played twice), with each trial 30 seconds long. The order of presentation of the practice trials and test trials was randomized for each participant.

The musical excerpts were drawn from the MIREX 2006 Audio Beat Tracking database in which musical excerpts had been annotated for beat locations by 30 listeners who tapped along to the music[130]. We chose these four MIREX clips that represent different music genres with different tempos and tapping difficulty: track 1 (“You're the First, the Last, My Everything” by Barry White), track 3 (“El Contrapunto” by Los Mensajeros de La Libertad), track 7 (“Le Sacre du Printemps” by Stravinsky), and track 19 (“Possessed to Skate” by Suicidal Tendencies) of the MIREX training set (respectively). Based on the annotations in[130], we identified the target beat locations from those consistently produced by the annotators. We performed kernel density estimation with a kernel width of 20 msec; this provided an estimate of the probability of

942 producing a response in any given time. The peaks of the probability density were
943 located using Matlab's findpeaks function with the following parameters:
944 'MinPeakHeight', 0.11/ts, 'MinPeakProminence',0.11/ts, 'MinPeakDistance',100 msec,
945 where ts is the number of responses in the clip. Beat locations were extracted from the
946 entire 30 seconds of the clip and used as the reference location for computing the
947 asynchrony. To help participants find the beat and eliminate potential ambiguity of
948 tapping at half- or double-time the tempo, a metronome marking the beats in the first 11
949 seconds of the clip were added to the stimulus (as commonly used in this type of
950 tapping paradigm). Additional technical details are provided in the Supplementary
951 Notes, and Supplementary Figure 2 illustrates the instructions for participants.
952
953 *Data Analysis.*
954 **Beat synchronization task performance: Tapping accuracy analysis**
955 Let S_t and R_t be the stimulus and response onsets, respectively. In case of the
956 metronome S_t are the metronome onset (practice phase) and for music clips S_t is the
957 target beat location based on the annotations. We define the asynchrony as a_t=R_t -R_t.
958 Based on prior work[131], we chose the standard deviation of the asynchrony (std(a_t)) as
959 our main target interest variable, as this appears to be a robust measure of individual
960 performance and tightly linked to musical abilities[132]. We used metronome onsets to
961 mark the beat metric level in an unambiguous way[133]. We emphasize that the
962 metronome onsets were only physically present during the beginning and end of each
963 clip. We used only the participant-produced asynchronies during the epoch at beats in
964 which the guiding metronome was *not* present, in order to test the ability of the

965 participants to synchronize to music without the metronome sounds (results were nearly
966 identical when we included all onsets including the one were physical metronome
967 onsets were present). For the main test scores, we used the asynchronies computed
968 relative to the virtual beat locations computed from prior human annotators in MIREX.

969 **Regression analyses**

970 In accordance with the OSF preregistration, we examined whether responses to
971 self-reported beat synchronization phenotype were associated with objectively-
972 measured tapping accuracy, other self-reported measures of rhythm ability, confidence,
973 and/or musical sophistication using logistic regression and McFadden's R^2 (for H1, H2a,
974 H3, and H5) and linear regression (for H1a and H2b). Likewise, we used linear
975 regression to examine potential replication of cross-trait associations uncovered by
976 genetic analyses (H4a-d), to examine whether musical background interacted with the
977 above associations (H6). Analyses were conducted in R version 3.5.1[134]. As described
978 in our preregistration, individuals were recruited using MTurk and were included unless
979 they failed and attention check item or abandoned the experiment before completing the
980 study (N=1,412). Usable tapping data was available for n=542 individuals. The majority
981 of exclusions were due to technical reasons detected by REPP's signal processing
982 pipeline during the practice trials (e.g., poor signal, noisy environment, wearing
983 headphone, issues with laptop microphone, or people not tapping at all), but some
984 additional subjects (n=19) were excluded for not having enough usable trials during data
985 analysis. Missing covariates were handled using pair-wise deletion. Exclusion criteria
986 are detailed in the Supplementary Notes.
987

988 **GWAS of beat synchronization.**

989 GWAS sample.

990 Genome-wide association study summary statistics were generated from data
991 acquired by personal genetics company 23andMe, Inc. Phenotypic status was based on
992 responses to an English-language online questionnaire in which individuals self-
993 reported “Yes” (cases) or “No” (controls) to the question ‘Can you clap in time with a
994 musical beat?”. Individuals who responded “I’m not sure” were excluded from the
995 genomic dataset as their data was not available. The GWAS included a total of 555,660
996 cases and 51,165 controls (total N=606,825, mean age(SD)=52.09(18.5),
997 prevalence=92%), all of European ancestry; age range breakdown is provided in Table
998 1. All individuals provided informed consent according to 23andMe’s human subject
999 protocol, which is reviewed and approved by Ethical & Independent Review Services, a
1000 private institutional review board (http://www.eandireview.com).
1001

1002 *Genotypes and QC.*

1003 The National Genetics Institute (NGI) performed the DNA extraction and
1004 genotyping on saliva samples for the 23andMe GWAS. Overall, there were five
1005 genotyping platforms and subjects were genotyped on only one of them. The v1 and v2
1006 platforms had variants of the Illumina HumanHap550+ BeadChip, including
1007 approximately 25,000 custom SNPs selected by 23andMe, with a total of about 560,000
1008 SNPs. The v3 platform had variants of the Illumina OmniExpress+ BeadChip, with
1009 custom content to improve the overlap with the v2 array, with a total of about 950,000
1010 SNPs. The v4 platform covered about 570,000 SNPs, providing extra coverage of

1011 lower-frequency coding variation. The v5 platform, in current use, is based on an
1012 Illumina Infinium Global Screening Array (~640,000 SNPs) supplemented with ~50,000
1013 SNPs of custom content. In cases where samples did not reach the 98.5% call rate, the
1014 sample was re-genotyped. When analyses failed repeatedly, then customers were re-
1015 contacted by 23andMe customer service to provide additional samples.

1016 23andMe restricted participants to a set of unrelated individuals of European
1017 ancestry, determined through an analysis of local ancestry[135]. Relatedness was defined
1018 using a segmental identity-by-descent (IBD) estimation algorithm[136]. Imputation was
1019 conducted by combining the May 2015 release of 1000 Genomes Phase 3
1020 haplotypes[137] with the UK10K imputation reference panel[138] to create a single unified
1021 imputation reference panel. Phasing was conducted using an internally-developed tool,
1022 Finch, which uses the Beagle graph-based haplotype phasing algorithm[139] for platforms
1023 V1 to V4 while for the V5 platform a similar approach was used with a new phasing
1024 algorithm, Eagle2[140]. SNPs with a Hardy-Weinberg $p<10^{-20}$, or a call rate of <90% were
1025 flagged. SNPs were also flagged if they were only genotyped on their 'V1' and/or 'V2'
1026 platforms due to small sample size and also if SNPs had genotype date effects. Finally,
1027 SNPs were also flagged if they had probes matching multiple genomic positions in the
1028 reference genome[136–140].

1029

1030 *GWAS.*

1031 GWAS was conducted using logistic regression under an additive genetic model,
1032 while adjusting for age, sex, the top five principal components of ancestry in order to
1033 control for population stratification, and indicators for genotype platforms to account for

1034 batch effects. We excluded SNPs with Minor Allele Frequency (MAF) <0.01, low
1035 imputation quality (R^2<0.3) and indels, resulting in 8,288,850 SNPs in the GWAS
1036 summary statistics. SNPs within the X chromosome were further excluded, resulting in
1037 8,076,862 SNPs for subsequent analyses unless otherwise indicated.
1038
1039 **Statistical analyses**
1040 *FUMA-based analyses.* The FUMA[60] web application was used on the Genome-
1041 Wide Association summary statistics to identify genomic loci along with the "sentinel"
1042 SNPs that were independent in our analysis with a genome-wide significant P-value (<5
1043 x 10^{-8}) that are in approximate linkage disequilibrium (LD) with each other at r^2<0.1 and
1044 to generate Manhattan plots and Quantile-Quantile plots.
1045 Gene-based analysis and gene-set analysis was performed with MAGMA (v1.08)
1046 using FUMA (v1.3.4) and the association analysis summary statistics. Gene expression
1047 data analysis was obtained from GTEx v8 (https://www.gtexportal.org/home/) integrated
1048 by FUMA. More specifically, the gene expression values were log2 transformed average
1049 RPKM per tissue type after winsorization at 50 based on GTEx RNA-seq data. Tissue
1050 expression analysis was performed for 53 tissue types where the result of gene analysis
1051 was tested for one side while conditioning on average expression across all tissue
1052 types.
1053
1054 *LD score regression and genetic correlations.* SNP-heritability was computed with LD
1055 Score regression software[64], and heritability estimates were adjusted to the liability
1056 scale based on population prevalence of poor rhythm of 3.0%-6.5% (Supplementary

1057 Table 3, Supplementary Notes). We partitioned heritability of beat synchronization by 52
1058 broad functional categories (Supplementary Table 7), using stratified LD score
1059 regression[64,67] (Bonferroni-corrected significance level of $p=9.6x10^{-4}$).
1060 We further investigated cell-type-specific and tissue-specific enrichments with
1061 LDSC-SEG (LDSC Specifically Expressed Genes)[67], using a total of 697 gene sets (3
1062 Cahoy gene sets, 205 Multi-tissue gene expression sets and 489 Multi-tissue chromatin
1063 sets from the RoadMap Epigenomics and ENCODE datasets); the Bonferroni-corrected
1064 significance level for this analysis was $7.1x10^{-5}$ (Supplementary Table 8).
1065 The set of human accelerated regions (HARs) was taken from[69]. All variants in
1066 perfect LD (r^2 = 1.0 in 1000 Genomes European individuals) with variants in HARs were
1067 considered in the analysis. Similarly, variants tagging Neanderthal introgressed
1068 haplotypes were defined as in[141]. All variants in perfect LD with a Neanderthal tag SNP
1069 were considered Neanderthal variants. For each set, we performed stratified LDSC
1070 (v1.0.0) with European LD scores and the baseline LD-score annotations v2.1. The
1071 heritability enrichment is defined as the proportion of heritability explained by SNPs in
1072 the annotation divided by the proportion of SNPs in the annotation. Standard effect size
1073 (τ_c^*), which quantifies the effects unique to the annotation, is the proportionate change in
1074 per-SNP heritability associated with a one standard deviation increase in the value of
1075 the annotation, conditional on other annotations in the baseline v2.1 model[66]. To
1076 determine the expected number of overlaps between the N loci significantly associated
1077 with beat synchronization and HARs, we computed all overlaps between these sets of
1078 genomic regions (in hg19 coordinates) using bedtools2[142]. We then randomly shuffled
1079 the locations of HARs around the genome respecting their lengths and avoiding gaps in

1080 the genome assembly. We repeated this process 10,000 times and for each iteration
1081 computed the number of overlaps observed with the significantly associated loci. Based
1082 on this empirical distribution created with no association between the region sets, we
1083 computed the enrichment and p-value for the observed number of overlaps.
1084 Genetic correlations between beat synchronization and other complex traits were
1085 estimated using LDSC through LDHub v1.9.0 (http://ldsc.broadinstitute.org/ldhub/)[47]
1086 using publicly available GWAS summary statistics therein. In total, 764 traits were
1087 examined (Bonferroni corrected threshold = 6.5×10^{-5}).
1088
1089 *Beat synchronization Polygenic Score (PGS) prediction of musicianship*
1090 *Overview.* We examined whether beat synchronization polygenic scores (PGS)
1091 would be associated with musicianship in a health care context. Musicians cases were
1092 drawn from a recent phenome-wide study of 9,803 musicians[76] identified from keyword
1093 searches of patient electronic health records (EHRs) in Vanderbilt University Medical
1094 Center's de-identified research database (Synthetic Derivative). The phenotyping
1095 method was based on mining of clinical notes, utilizing 4 keywords and 449 regular
1096 expressions (i.e., "musician", "plays the piano"); see Supplementary Notes and[76] for
1097 details. Their method was validated with manually conducted chart review, with a
1098 positive predictive value (PPV) of 93%. Here we accessed the subset of n=1,753
1099 musicians that were also part of the BioVU database and had genotyped data on file, to
1100 test the hypothesis that higher PGS for beat synchronization would be associated with
1101 musicianship (i.e., higher likelihood of having musician-related keywords/regular
1102 expressions recorded in an individual's electronic health record).

1103 We only selected individuals of European ancestry with genetic data that met
1104 standard quality control thresholds, resulting in n=1,753 individuals (965 (55%) males,
1105 mean median age of record (SD)=44.3(22.5)) as musician "cases" and 65,147 controls
1106 (28698(44%) males, mean median age of record (SD)=48.3(22.3)). See Supplementary
1107 Notes for details on the phenotyping, the samples, genotyping, and QC.

1108 *Polygenic scores.* We used an IBD filter of 0.2 in order to include unrelated
1109 European samples of BioVU. PGS were generated using the beat synchronization
1110 GWAS summary statistics, using software PRS_CS[143]. Briefly, this method uses a
1111 Bayesian regression framework and places continuous shrinkage (CS) prior on SNP
1112 effect sizes; this method outperforms previous methods in terms of prediction accuracy
1113 especially when the training sample size is large[143], as is the case with the beat
1114 synchronization GWAS. The 1000genomes reference set was used. The PGS was
1115 standardized to have a mean of 0 and SD of 1.

1116 *Control traits in BioVU.* As negative control phenotypes we selected the following
1117 traits: Iron deficiency anemias (phecode:280, cases=4,594, controls=62,306),
1118 carcinoma in situ of skin (phecode:172.3, cases=523, controls=66,377), and cancer of
1119 the brain (phecode:191.11, cases=970, controls=65,930).

1120 *Data analysis.* We conducted a logistic regression where the outcome variable
1121 was keyword "musician" (yes vs no) and the predictor variable was PGS for beat
1122 synchronization, while also adjusting for median age, sex, 10 Principal Components and
1123 genotyping batch. The same process was followed when the outcome variables were
1124 iron deficiency anemias, carcinoma in situ of skin and cancer of the brain (cases vs.
1125 controls).

1126

Acknowledgments: We are grateful to 23andMe participants for their contribution to the study, Nancy Cox and Simon Fisher for suggestions and insight throughout the process, Navya Thakkar for assistance with graphics, and Miriam Lense, Matthew D. Morrison, and Wim Pouw for thoughtful discussions. We would also like to thank Michaela Novakovic, Yune Lee, and Duane Watson for input during previous stages of the project, and Vanderbilt Trans-Institutional Programs for sparking the initial collaboration. Members of the 23andMe Research Team are: Michelle Agee, Stella Aslibekyan, Adam Auton, Robert K. Bell, Katarzyna Bryc, Sarah K. Clark, Sarah L. Elson, Kipper Fletez-Brant, Pierre Fontanillas, Nicholas A. Furlotte, Pooja M. Gandhi, Karl Heilbron, Barry Hicks, Karen E. Huber, Ethan M. Jewett, Yunxuan Jiang, Aaron Kleinman, Keng-Han Lin, Nadia K. Litterman, Jennifer C. McCreight, Matthew H. McIntyre, Kimberly F. McManus, Joanna L. Mountain, Sahar V. Mozaffari, Priyanka Nandakumar, Elizabeth S. Noblin, Carrie A.M. Northover, Jared O'Connell, Steven J. Pitts, G. David Poznik, Anjali J. Shastri, Janie F. Shelton, Suyash Shringarpure, Chao Tian, Joyce Y. Tung, Robert J. Tunney, Vladimir Vacic, and Xin Wang.

Funding:

Research reported in this publication was supported by the National Institutes of Health Common Fund through the Office of the NIH Director and the Eunice Kennedy Shriver National Institute of Child Health & Human Development under award number DP2HD098859, and by the National Institute On Deafness And Other Communication Disorders under award numbers K18DC017383 and R01DC016977. JAC was supported by the National Institutes of Health (R35GM127087). The content is solely

1151 the responsibility of the authors and does not necessarily represent the official views of
1152 the NIH.
1153 The dataset used for the analyses described were obtained from Vanderbilt
1154 University Medical Center's BioVU which is supported by numerous sources:
1155 institutional funding, private agencies, and federal grants. These include the NIH funded
1156 Shared Instrumentation Grant S10RR025141; and CTSA grants UL1TR002243,
1157 UL1TR000445, and UL1RR024975. Genomic data are also supported by investigator-
1158 led projects that include U01HG004798, R01NS032830, RC2GM092618,
1159 P50GM115305, U01HG006378, U19HL065962, R01HD074711; and additional funding
1160 sources listed at https://victr.vumc.org/biovu-funding/. Also, The Genotype-Tissue
1161 Expression (GTEx) Project was supported by the Common Fund of the Office of the
1162 Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH,
1163 and NINDS. GTEx data used for the analyses described in this manuscript were
1164 obtained from: the GTEx Portal on 07/26/19 and dbGaP accession
1165 number phs000424.vN.pN on 07/26/19 .
1166
1167
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Competing interests: JFS, DH, and members of the 23andMe Research Team are employees of 23andMe, Inc., and hold stock or stock options in 23andMe. All other authors declare no competing interests.

1199 **Data and materials availability:** The full GWAS summary statistics for the 23andMe
1200 dataset will be made available through 23andMe to qualified researchers under an
1201 agreement that protects the privacy of the 23andMe participants. Please visit
1202 research.23andme.com/collaborate/#publication for more information and to apply to
1203 access the data. The data and code from the phenotype validation studies, and all of
1204 the code from the post-GWAS analyses, are also available upon reasonable request.
1205

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1

Tables

Table 1. Sample demographics for each of the three cohorts (GWAS, Phenotype Experiment 1, and Phenotype Experiment 2).

GWAS Sample by Phenotype group (response to Clap-to-beat question)

	Cases (Yes)	Controls (No)
Total	555660	51165
Males	226188	23998
Females	329472	27167
18 to 30 years old	57898	5186
30 to 45 years old	135168	12909
45 to 60 years old	150939	13312
60 years old and over	211655	19758

Phenotype Validation Experiment 1 – rhythm perception

Full sample who provided demographics	N	Mean Age in years (for N=722 who reported demographics)	SD Age
Total	722	36.03	10.98
Males	386	34.86	10.74
Females	332	37.49	11.07

Phenotype Validation Experiment 2 – beat production and cross-trait

Full sample	N	Mean Age in years	SD Age
Total	1412	36.34	11.93
Males	678	35.53	11.12
Females	728	37.15	12.61
Subset with valid tapping data	n	Mean Age in years	SD Age
Total	542	35.24	11.39
Males	241	35.02	10.62
Females	300	35.43	12.00

Table 2. Genomic loci and sentinel SNPs significantly associated with beat synchronization in the primary GWAS. Further details (e.g., chromosomal location) are provided in Supplementary Table 2.

Genomic Locus	Sentinel SNP	chr	A1	MAF	OR	SE	p-value	gene symbol
11	rs848293	2	G	0.42228	0.94	0.007	9.23E-18	*VRK2*
26	rs62340585	4	G	0.20695	0.94	0.008	1.81E-14	*GPM6A*
13	rs10168817	2	G	0.49299	0.95	0.007	1.94E-14	*NA*
20	rs10779987	3	T	0.38175	0.95	0.007	2.21E-14	*GBE1*
28	rs28392605	5	G	0.33904	0.95	0.007	8.93E-14	*NA*
45	rs1832909	9	T	0.40687	1.05	0.007	1.78E-13	*NA*
2	rs34762587	1	T	0.31379	1.05	0.007	2.25E-13	*FOXO6*
60	rs7542	16	G	0.46184	0.95	0.007	2.41E-13	*MAPK3*
5	rs10875125	1	C	0.15305	0.93	0.009	2.61E-13	*DPYD*
35	rs9400241	6	C	0.28851	0.95	0.007	4.49E-13	*FOXO3*
64	rs4792891	17	T	0.34013	1.05	0.007	7.07E-13	*MAPT*
39	rs1468701	7	G	0.29172	0.95	0.007	3.62E-12	*SND1*
50	rs10848650	12	G	0.42192	1.05	0.007	6.04E-12	*SLC6A13*
29	rs2635634	5	T	0.45317	1.05	0.007	9.54E-12	*CDH12*
67	rs9626920	22	G	0.41282	1.05	0.007	1.04E-11	*MIRLET7BHG*
16	rs764299	2	G	0.26719	1.05	0.007	1.47E-11	*PLEKHM3*
43	rs10984506	9	T	0.36558	1.05	0.007	1.66E-11	*ANP32B*
53	rs1426371	12	G	0.25919	1.05	0.008	1.67E-11	*WSCD2*
58	rs12913592	15	T	0.3596	1.05	0.007	6.13E-11	*NA*
6	rs72700870	1	G	0.14377	0.94	0.009	1.42E-10	*MCL1*
34	rs9388171	6	G	0.47595	0.96	0.007	2.16E-10	*NA*
55	rs6572878	14	T	0.39477	0.96	0.007	3.48E-10	*HAUS4*
4	rs11210206	1	T	0.31286	0.96	0.007	3.93E-10	*NA*
28	rs72633496	5	T	0.43224	0.95	0.008	6.21E-10	*NA*
10	rs7586405	2	G	0.30559	1.04	0.007	7.19E-10	*PPP1CB*
63	rs3024293	17	T	0.23528	1.05	0.008	8.26E-10	*C1QL1*
1	rs2061843	1	G	0.4001	0.96	0.007	1.19E-09	*CSMD2*
19	rs1349028	3	T	0.25977	0.95	0.008	1.54E-09	*EIF4E3*
25	rs4443239	4	T	0.2463	1.05	0.008	1.68E-09	*C4orf27*
33	rs1901739	5	T	0.47772	1.04	0.007	2.14E-09	*NA*
7	rs55678522	1	G	0.21629	0.95	0.008	2.25E-09	*LRRN2*
61	rs8079923	17	T	0.25309	1.05	0.008	2.88E-09	*AKAP10*
62	rs7501911	17	T	0.18191	0.95	0.009	3.34E-09	*NLK*
66	rs6087848	20	G	0.44304	0.96	0.007	3.40E-09	*POFUT1*
54	rs10744255	12	G	0.23229	0.96	0.008	4.24E-09	*NA*
31	rs13163173	5	C	0.16597	0.95	0.009	4.51E-09	*MEF2C*
3	rs2819333	1	T	0.37068	1.04	0.007	4.54E-09	*PTPRF*
51	rs2453873	12	G	0.22254	0.95	0.008	5.17E-09	*NA*
27	rs67264739	5	G	0.27395	0.96	0.007	5.54E-09	*ADCY2*
56	rs2284901	14	G	0.37485	1.04	0.007	6.48E-09	*AKAP6*
32	rs1596431	5	T	0.19182	1.05	0.008	7.42E-09	*NA*
44	rs10978661	9	T	0.12006	0.94	0.01	7.74E-09	*ZNF462*
23	rs4263335	4	G	0.49483	1.04	0.007	8.74E-09	*JAKMIP1*
48	rs7939759	11	T	0.23981	1.05	0.008	1.23E-08	*CTSF*
65	rs9710427	19	G	0.41536	1.04	0.007	1.32E-08	*TECR*
21	rs12638746	3	G	0.33546	0.96	0.007	1.37E-08	*EPHA3*
59	rs12909047	15	G	0.48251	1.04	0.007	1.49E-08	*UBL7*
46	rs2505344	10	G	0.17674	0.95	0.009	1.51E-08	*EPC1*
24	rs67816799	4	C	0.38188	1.04	0.007	1.56E-08	*CCSER1*

15	rs10932201	2	G	0.46351	1.04	0.007	1.59E-08	*CREB1*
49	rs526904	11	T	0.34865	0.96	0.007	1.60E-08	*PICALM*
9	rs6548147	2	T	0.4402	1.04	0.007	2.05E-08	*TSSC1*
52	rs10877461	12	G	0.29968	0.96	0.008	2.44E-08	*NA*
41	rs11996434	8	G	0.27037	1.04	0.008	2.61E-08	*NA*
40	rs1996148	8	G	0.31961	0.96	0.007	2.69E-08	*PEBP4*
47	rs10885458	10	G	0.28314	0.96	0.007	2.69E-08	*NA*
17	rs191373913	2	T	0.43899	0.96	0.007	2.74E-08	*NGEF*
38	rs12056186	7	C	0.42875	0.96	0.007	2.93E-08	*ORC5*
42	rs7856850	9	C	0.22184	0.96	0.008	3.07E-08	*PTPRD*
36	rs13197257	6	T	0.27444	0.96	0.007	3.23E-08	*PTPRK*
14	rs10497355	2	T	0.46078	1.04	0.007	3.43E-08	*UBR3*
12	rs11692449	2	T	0.37522	1.04	0.007	3.45E-08	*XPO1*
30	rs4704043	5	T	0.2827	1.04	0.007	3.65E-08	*TNPO1*
18	rs43182	3	T	0.13443	1.06	0.01	3.80E-08	*PTPRG*
57	rs62014217	15	G	0.20132	0.96	0.008	3.91E-08	*HERC1*
8	rs476141	1	T	0.49868	1.04	0.007	4.49E-08	*NA*
37	rs2849543	6	G	0.41591	1.04	0.007	4.60E-08	*PARK2*
22	rs571760466	3	C	0.27511	0.96	0.007	4.81E-08	*LSAMP*

Abbreviations: SNP=Single Nucleotide Polymorphism, chr=Chromosome, A1=effect allele, MAF=Minor Allele Frequency, OR=Odds Ratio, S.E.=Standard Error, Notes: Gene symbol is based on HUGO (HGNC). These are all genes annotated to SNPs in r2> 0.1 with the lead SNP; sentinel SNP in a given locus refers to independent SNP from FUMA. The SNPs were mapped to genes based on ANNOVAR annotation and on being physically located inside a protein coding gene using 10kb window. NA=when the SNP is not within the 10kb window of a gene.

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