

SCIENTIFIC REPORTS

OPEN

Convergent evidence for the molecular basis of musical traits

Jaana Oikkonen^{1,2}, Päivi Onkamo², Irma Järvelä¹ & Chakravarthi Kanduri¹

Received: 01 July 2016
Accepted: 25 November 2016
Published: 22 December 2016

To obtain aggregate evidence for the molecular basis of musical abilities and the effects of music, we integrated gene-level data from 105 published studies across multiple species including humans, songbirds and several other animals and used a convergent evidence method to prioritize the top candidate genes. Several of the identified top candidate genes like *EGR1*, *FOS*, *ARC*, *BDNF* and *DUSP1* are known to be activity-dependent immediate early genes that respond to sensory and motor stimuli in the brain. Several other top candidate genes like *MAPK10*, *SNCA*, *ARHGAP24*, *TET2*, *UBE2D3*, *FAM13A* and *NUDT9* are located on chromosome 4q21-q24, on the candidate genomic region for music abilities in humans. Functional annotation analyses showed the enrichment of genes involved in functions like cognition, learning, memory, neuronal excitation and apoptosis, long-term potentiation and CDK5 signaling pathway. Interestingly, all these biological functions are known to be essential processes underlying learning and memory that are also fundamental for musical abilities including recognition and production of sound. In summary, our study prioritized top candidate genes related to musical traits.

Music perception and performance represent complex cognitive functions of the human brain. Research on families, twins and newborns, neurophysiological studies and more recently genomics studies have suggested that the abilities to perceive and practice music have a biological background^{1–5}. Over the past decade, several studies ranging from candidate gene level to genome-wide scans have investigated the molecular basis of musical traits in humans. For example, conventional genetic approaches such as genome-wide linkage scans, association studies^{3,6–8} and CNV studies^{9,10} have shown that musical aptitude is linked to regions that contain genes affecting development and function of auditory pathway and neurocognitive processes. Studies of genome-wide RNA expression profiles have revealed that listening and performing music enhanced the activity of genes related to dopamine secretion and transport, neuronal plasticity, learning and memory^{11,12}. Recently, positive selection regions associated with musical aptitude have been shown to contain genes that affect hearing, language development, birdsong and reward mechanism¹³. Despite these independent findings, aggregate evidence for the molecular basis of musical traits remains lacking.

Musical abilities in humans are based on sound perception and production that are well preserved in evolution^{14–16}. Even birdsong is known to have musical features: it is a combination of rhythms, pitches, and transitions that induce emotional responses¹⁷ and vocal learning show similar features between songbirds and humans¹⁸. In zebra finches, vocal learning happens during sensitivity period from 25 to 65 dph (days post-hatch)¹⁹. Similar sensitivity period to learn music and language has been reported in humans²⁰ and for music preference in mice²¹. Convergent evolution of hearing genes has been found in echo-locating bats and dolphins²². Interestingly, mammals, including modern humans, have been shown to share similar inner ear structures even with insects²³. A shared background of sound perception and production between evolutionarily as distant species as humans and songbirds has been found in our previous studies, where several homologous genes known to affect song learning and singing in songbirds were up-regulated after music perception and performance in humans^{11,12}. All these evidence suggest a high evolutionary conservation, or convergent evolution, of molecular mechanisms related to sound perception and production. Therefore, data from relevant animal models like songbirds might be used as an additional layer of evidence when outlining the contours of the genetic landscape underlying musical traits in humans.

To obtain convergent evidence for the molecular basis of musical traits, we integrated gene-level data from a wide range of studies including genome-wide linkage and association studies, gene expression studies, candidate gene studies and other molecular studies in both humans and relevant animal models. A similar strategy has

¹Department of Medical Genetics, University of Helsinki, P.O. Box 720, 00014 University of Helsinki, Finland.

²Department of Biosciences, University of Helsinki, P.O. Box 56, 00014 University of Helsinki, Finland. Correspondence and requests for materials should be addressed to J.O. (email: jaana.oikkonen@helsinki.fi)

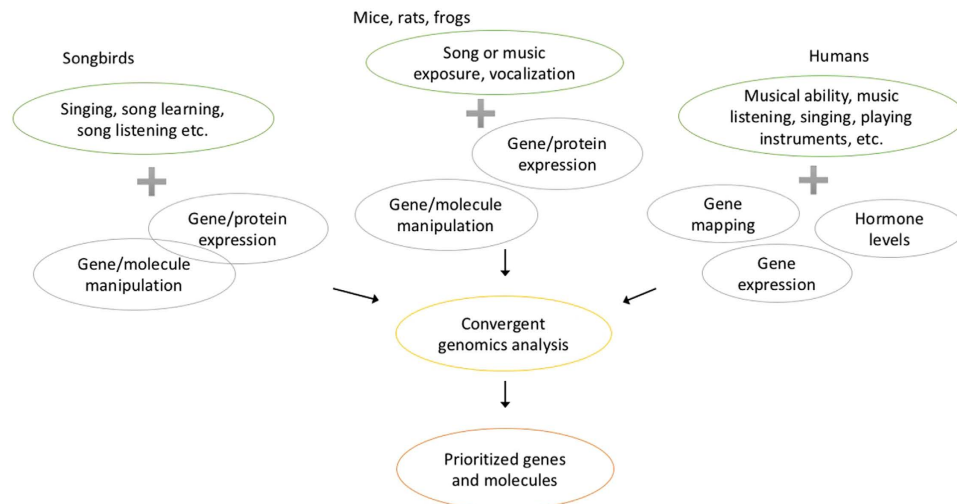


Figure 1. Studies included for the CE analysis included a variety of methods and animals. The figure shows the types of studies included from the different species. The music-related traits in studies using different animals varies as well as the used molecular evidence levels. All molecular evidence from these different types of studies was mapped to human genes and integrated in the CE analysis.

earlier been used successfully to identify top candidate genes underlying several neuropsychiatric diseases^{24–26}. Here, we curated a database of 105 published studies with 7895 genes by integrating our own and other human studies as well as animal studies related to music and musical abilities including studies on songbirds, mice and several other species. We used the convergent evidence method (CE) implemented by one of the authors (C.K.) in GenRank Bioconductor package to prioritize the candidate genes. Functional enrichment analysis of the prioritized genes suggests that the top candidate genes are known to affect cognition, learning, memory, excitation of neurons, the quantity of catecholamine and long-term potentiation.

Results

Study database. We retrieved a total of 331 articles related to music, of which 105 articles were shortlisted after filtering out irrelevant articles. The retained articles included biomarker and candidate gene studies and genome-wide studies at both DNA- and RNA-level across several species including humans, songbirds and mice (Fig. 1). The summary statistics of the study database are shown in Table 1. All the chosen studies were listed in the Supplementary Data and in Tables S1–S3. The genes and molecules identified in animal model studies were translated into human genes through homologs. A total of 7895 genes and biomarkers were identified at least once from the 105 published studies related to musical abilities (Table S4). Nearly a quarter of the genes (1755 genes) were found within linkage regions (Fig. 2).

Top candidate genes. The CE method ranked *EGR1*, cortisol, *FOS*, *FOXP2*, *ARC*, dopamine and *BDNF* as the top candidate genes and molecules related to music (Table 2, Supplementary Data). Among the top hits, some genes like *EGR1*, *FOXP2*, *BDNF* and *ARC* have not yet been found in human studies, while some other genes like *PHIP*, *MAPK10*, *SNCA*, and *ARHGAP24*, received top ranks because of major evidence from human studies. The top candidate genes were evenly distributed across genomic locations, except for an enrichment of seven genes on human chromosome 4q21–q24 (*MAPK10*, *SNCA*, *ARHGAP24*, *TET2*, *UBE2D3*, *FAM13A* and *NUDT9*), which is the region indicated in several gene-mapping studies.

To gather information whether the top genes relate only to a subset of the traits related to music, we analysed the studies in three phenotype categories: music listening, musical ability and music practice. The *EGR1* gene was among the highly ranked genes in all three categories, whereas no other molecule exhibited a similar pattern. Majority of the top genes were related to both music practice and listening (Table 2, Supplementary Fig. S1), with some exceptions: *PHIP*, noradrenalin and *NR4A2* were ranked among the top molecules in the whole sample as well as within music listening studies, but not within music practice (e.g. singing) related studies. Vice versa, genes like *DUSP1*, *PKIA* and *DOPEY2* were highly ranked in the whole sample as well as in music practice studies, but not in music listening or musical ability studies. Only a few top genes were most evident in the musical ability-related studies. These included the *GRIN2B* and *ARHGAP24* genes. Notably, studies related to each of the subphenotypes have also differences regarding the type of the biological samples and utilized animals: for example, there were more DNA-level and human studies related to musical ability than to music listening or music practice (Supplementary Data).

Functional annotation. We studied the functional annotations of the top ranked genes through functional class enrichment, pathway and interaction network analyses. Functional enrichment analysis of the top 40 ranked genes revealed enrichment of genes related to cognition, memory, learning, excitation of neurons, the quantity of catecholamine, apoptosis of neurons, and long-term potentiation (p -values $< 4 \times 10^{-10}$), in the order of significance (p -value) (Table 3). ~40% of the top 40 candidate genes were related to cognition (Supplementary Table S4,

Species	# studies	DNA: candidate + (genome-wide)	RNA:candidate + (genome-wide)	Other molecular information	Phenotype related to musical ability	Phenotype related to music listening	Phenotype related to music practise
Human	35	5 + (5)	1 + (3)	22	16	22	8
Songbird	55	—	16 + (8)	32	19	27	34
Other animals	15	1 + (—)	1 + (3)	12	1	10	5

Table 1. Summary statistics of the study database. Some studies include evidence from multiple molecular levels or phenotypes, and thus contribute to multiple subcategories. Phenotypes related to music practise can include for example singing, vocalization and instrument playing as phenotype. Musical ability related studies in non-human species consists mostly of memory and sensitivity period related studies. Many studies reported protein or hormone related evidence (contributing to “other molecular information”). No DNA-level studies on songbirds were discovered. Numbers in brackets in 3rd and 4th columns correspond to the number of genome-wide studies.

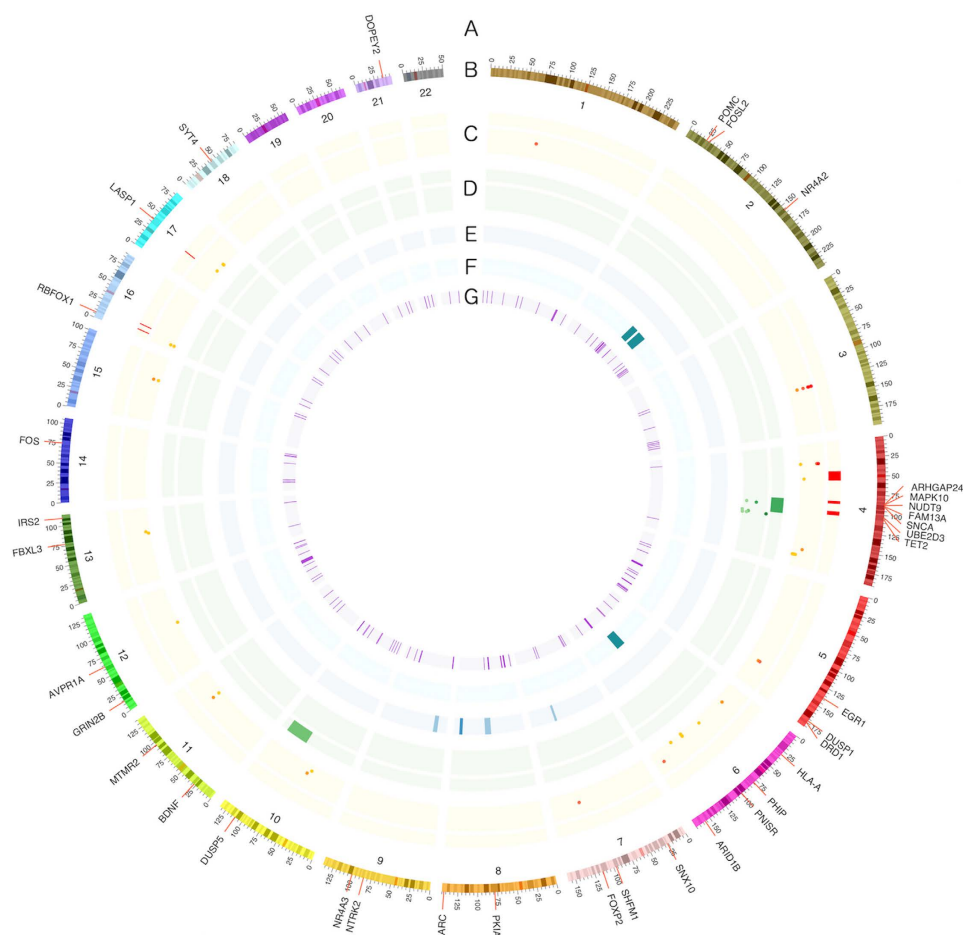


Figure 2. Human gene mapping results of musical abilities and the top 40 genes from the CE analysis. The top genes (A) are shown on the genomic context (B: coordinates for every chromosome as Mb). Published gene mapping results are shown with heat map bars (linkage) or dots (association): included results by (C) Oikkonen, *et al.*³, (D) Park, *et al.*⁷, (E) Theusch, *et al.*⁸ and (F) Gregersen, *et al.*⁵⁸. The innermost circle shows regions identified by selection signature methods (G) by Liu, *et al.*¹³.

Supplementary Fig. S2). Pathway analysis showed enrichment of genes related to CDK5 signaling pathway (p-value 2.3×10^{-8} , 6 molecules, Supplementary Fig. S3) that is known to affect neurite outgrowth and neuronal migration²⁷.

Further functional analysis with subphenotypes showed enrichment of many of the same functions, including learning, behaviour, and apoptosis of neurons. Additionally, the ability-related top molecules (N = 29) now picked up neuronal cell death related functions as well as development of head and bone marrow as most prominent (Supplementary Table S5). The listening-related molecules (N = 18) showed enrichment of lipid synthesis, proliferation of muscle cells, and memory (Supplementary Table S6). The practice-related top molecules (N = 29)

Gene information		Result	Number of studies where indicated					
Gene symbol	Genomic location in humans	CE Score	Humans	Songbirds	Other	Practise [*]	Listening [*]	Ability [*]
<i>EGR1</i>	5q23-q31	0.219	—	29	1	13	19	7
Cortisol	—	0.169	14	—	—	2	13	1
<i>FOS</i>	14q24.3	0.149	1	15	3	7	13	4
<i>FOXP2</i>	7q31	0.102	—	12	2	13	—	6
<i>ARC</i>	8q24.3	0.067	—	8	1	4	3	—
Dopamine	—	0.059	1	3	3	4	6	1
<i>BDNF</i>	11p14.1	0.056	—	4	3	4	3	—
<i>Noradrenalin</i>	—	0.052	3	1	1	—	5	1
<i>GRIN2B</i>	12p13.1	0.049	1	4	1	3	2	3
<i>SYT4</i>	18q12.3	0.049	1	5	—	4	1	1
<i>PHIP</i>	6q14	0.047	2	3	—	1	2	2
<i>MAPK10</i>	4q22-q23	0.047	2	3	—	3	1	2
<i>DRD1</i>	5q34-q35	0.046	—	4	2	5	1	1
<i>SNCA</i>	4q21.3-q22	0.045	3	—	1	3	1	1
<i>NR4A3</i>	9q22	0.044	—	6	—	2	4	—
<i>IRS2</i>	13q34	0.044	—	6	—	3	3	—
<i>ARHGAP24</i>	4q22.1	0.043	3	1	—	2	1	2
<i>MTMR2</i>	11q22	0.043	1	4	—	3	1	1
<i>NR4A2</i>	2q22-q23	0.043	1	3	1	1	3	1
<i>DUSP1</i>	5q35.1	0.042	1	4	—	4	1	—
<i>DUSP5</i>	10q25	0.042	1	4	—	3	2	1
<i>PKIA</i>	8q21.13	0.041	1	4	—	3	1	1
<i>PNISR</i>	6q16.3	0.040	1	4	—	2	2	1
<i>Estradiol</i>	—	0.040	1	4	—	1	4	2
<i>TET2</i>	4q24	0.039	2	2	—	2	1	2
<i>UBE2D3</i>	4q24	0.039	2	2	—	3	—	2
<i>FAM13A</i>	4q22.1	0.039	2	2	—	2	1	2
<i>NUDT9</i>	4q22.1	0.039	2	2	—	3	—	2
<i>DOPEY2</i>	21q22.2	0.038	2	2	—	3	—	1
<i>NTRK2</i>	9q22.1	0.038	—	4	1	3	2	—

Table 2. Top 30 candidate genes related to music identified by CE. CE score is calculated as weighted mean from the number of layers where the molecule has been detected. The following columns show the number of studies where the molecule has been detected, classified by species and subphenotypes. More information on the cellular location and music-related brain regions can be found from Supplementary Table S8. The full list of ranked molecules can be seen in Supplementary Data. *There can be multiple phenotypes per study or the study phenotype may belong to multiple subcategories.

showed enrichment of epileptic seizure and transformation of fibroblast cell lines (Supplementary Table S7; p -values $< 5 * 10^{-9}$). Consistently with previous results, the CDK5 signaling was shown with music listening and practice. Overall, the results were more similar between listening and practice whereas ability-related molecules showed very different pattern of enrichment.

Network analysis revealed enrichment of interactions forming four non-overlapping networks each including 8–10 of the top-ranked genes. The most significant network was related to behaviour (Supplementary Fig. S4), the biological impact of the other three networks was less clear (Supplementary Figs S5–S7). These networks may reveal subsets of the top molecules that work together. The identification of four non-overlapping networks may indicate several separate pathways affecting music-related traits. For example, all of the top genes within the second largest network (Supplementary Fig. S6) were indicated in studies considering music practice. Interestingly, also the genes related to CDK5 signaling pathway were enriched in the most significant interaction network related to behaviour.

Upstream regulator analysis suggested cocaine, noradrenalin and calcineurin as possible upstream regulators (p -value $< 7 * 10^{-12}$) of many of the top ranked genes. Regarding subphenotypes, cocaine and calcineurin were supported by the listening and practice-related molecules. This shows interconnections between the top ranked genes, as noradrenalin itself was one of the top molecules. Noradrenalin is known to increase expression of *BDNF*, *DUSP1*, *EGR1*, *FOS*, *FOSL2*, *IRS2*, *NR4A3* and *POMC* and decrease expression of *GRIN2B*, identified in this study. It works as a hormone and neurotransmitter causing arousal, anxiety, and attention. Emotional arousal is known to affect memory and synaptic plasticity and noradrenalin is a major transmitter of these effects²⁸.

Disease or function	p-value/ top 40	# molecules/ top 40	p-value/ ability	p-value/ listening	p-value/ practice
Cognition	1.7×10^{-16}	16	—	—	8.3×10^{-8}
Memory	2.0×10^{-14}	14	—	8.5×10^{-11}	5.6×10^{-6}
Learning	2.5×10^{-14}	12	1.4×10^{-4}	2.6×10^{-12}	8.2×10^{-6}
Excitation of neurons	5.4×10^{-12}	8	—	7.8×10^{-7}	1.6×10^{-7}
Quantity of catecholamine	3.1×10^{-11}	9	—	3.9×10^{-9}	—
Apoptosis of brain	6.2×10^{-11}	9	—	—	2.1×10^{-7}
Epilepsy	7.9×10^{-11}	10	—	—	—
Behavior	1.2×10^{-10}	8	2.2×10^{-4}	1.0×10^{-9}	1.1×10^{-5}
Transcription	1.6×10^{-10}	12	—	7.5×10^{-8}	—
Transcription of RNA	1.9×10^{-10}	21	—	3.5×10^{-7}	1.6×10^{-7}
Quantity of cells	2.1×10^{-10}	22	—	3.6×10^{-7}	1.2×10^{-3}
Apoptosis of striatal neurons	2.4×10^{-10}	21	—	1.1×10^{-4}	2.5×10^{-6}
Apoptosis of neurons	2.5×10^{-10}	7	1.0×10^{-5}	5.0×10^{-9}	9.0×10^{-6}
Long-term potentiation of brain	3.3×10^{-10}	10	—	—	—
Long-term potentiation	3.6×10^{-10}	10	—	3.9×10^{-9}	5.2×10^{-6}
Diabetes mellitus	4.2×10^{-10}	11	—	4.7×10^{-8}	—
Synthesis of D-glucose	5.4×10^{-10}	8	—	1.0×10^{-6}	—
Expression of RNA	6.9×10^{-10}	16	—	1.7×10^{-7}	2.8×10^{-8}
Cell death of brain cells	9.0×10^{-10}	22	—	—	5.1×10^{-7}
Glucose metabolism disorder	9.6×10^{-10}	10	—	—	—

Table 3. The most enriched functions within the top 40 molecules. The list of molecules related to each functions is available at Supplementary Table S4. The three rightmost columns show p-values for enrichment of the functions in the three subphenotypes: musical ability, music listening and music practice (analysis included 29, 18 and 29 molecules, respectively).

Discussion

We were able to identify 105 molecular studies including music-related phenotypes. We prioritized the genes and molecules found in these studies to identify the most probable genes affecting musical ability and the effects of music. Overall, *EGR1* was the highest ranked gene. General cognition-related genes were enriched within the top ranked genes.

Musical abilities and several related traits have been studied in humans and multiple animal models using genetic methods ranging from single-gene to genome-wide studies. Over the past decade, numerous genomic regions, genes and biomarkers related to musical abilities, including for example music perception and performance, have been detected with varying levels of statistical significance. Here, for the first time, we obtained aggregate evidence for the molecular basis of musical traits that are shared between species.

Several of the top candidate genes like *EGR1*, *FOS*, *ARC*, *BDNF* and *DUSP1* are activity-dependent immediate early genes (IEGs) well known to be regulated by sensory and motor behaviours in the brain^{29,30}. These genes have been found to have essential roles in vocal learning and sound production in several animal studies^{29,30}. Especially the *EGR1* gene has repeatedly been shown to upregulate during song listening and singing in zebra finches and other songbirds (see for example Avey, *et al.*³¹, Drnevich, *et al.*³², Jarvis, *et al.*³³, Mello, *et al.*³⁴). Interestingly, *FOS* and *DUSP1* genes have an increased transcriptional activity in professional musicians after they played musical instruments¹¹. Other candidate genes like *FOXP2* and *GRIN2B* have been shown to be critical for vocal communication in songbirds and speech in humans^{35–38}. Moreover, *GRIN2B* is located in positive selection region of musical aptitude¹³.

Some of the top candidate genes have major evidence from animal studies (especially songbirds), with little or no evidence from human studies. The reasons for this can be several-fold such as tissue-specificity, species-specificity, and phenotype definition. Foremost, it is important to note that the majority of animal studies were carried out on brain tissue, while that is mostly inaccessible in humans. Second and noteworthy, we were not able to find genome-wide DNA studies from songbirds and reciprocally, there were relatively few genome-wide RNA studies in humans (Table 1) coupled with tissue-specific differences as discussed above. Third, the overall number of studies existing as of now is quite low, which is why the findings do not produce highly convergent results at this stage with any organism. Although we are interested in the shared molecular mechanisms behind musical abilities between species, we acknowledge that extrapolating genes found from animal models to human phenotypes carry limitations.

Among the top 40 candidate genes, seven genes (*MAPK10*, *SNCA*, *ARHGAP24*, *TET2*, *UBE2D3*, *FAM13A* and *NUDT9*) are located on human chromosome 4q21-q24 (Fig. 2), the region showing strongest evidence for linkage and association with musical abilities^{3,7,39}. All these seven genes show major evidence from human studies, while receiving only supporting evidence from animal studies (Table 2). The other genes like *PHIP*, *DOPEY2*, *AVPR1A* and *POMC* that have been detected in human studies have not shown very strong evidence in individual studies. For example, *PHIP* has only been shown in one linkage analysis and one association analysis concerning humans

but it has also been indicated in songbird-studies for singing and song listening^{32,40}. However, our aggregated evidence now prioritizes these as the top candidate genes for musical abilities and effects of music. This demonstrates the strength of the CE method to prioritize candidate genes from multiple independent studies, even when some studies are limited in statistical power.

On the other hand, genes like *UGT8*, *GATA2* and *PCDH7*, which were the most statistically significant findings in previous human genome-wide linkage and association studies, were not ranked among the top candidate genes here; each of these three genes were associated with music-related traits in only one study. This is probably due to the inherent nature of the method to identify only the genes with multiple independent lines of evidence. Additionally, the number of genome-wide studies about musical ability is still quite low and reciprocally, most of the animal studies have not been designed to detect specifically musical ability-related traits. However interestingly, *GATA2* and *PCDH7* are known to express in the inner ear. Previous evidence suggested a role for auditory pathway genes in musical abilities, but this was not evident through the top ranked genes. This may result from the lack of musical traits-related expression data from the inner ear and most other hearing-related tissues in this study, as well as from the wide spectrum of phenotypes included, not all related to perceptual skills. Thus, it can be too early to rule out the possibility that these genes have function in musical abilities. Additionally, the method does not take into account the difference in probabilities within each study (because it was not available for all studies) but all evidence from the same study gain same weight. For example, even though *UGT8* was supported by coding mutation, it gained same score as the other association-supported genes from the same study⁷.

Musical abilities (irrespective of the species) include the abilities to recognize, memorize and produce sound, which requires higher cognitive functions like learning and memory. Thus, the enrichment of candidate genes related to these functions in our study was not surprising. Moreover, an abundance of neuroscientific studies has demonstrated enhanced cognitive performance, learning and memory after training music for longer time^{41–43}. Further, the enrichment of genes related to neuronal excitation, neuronal apoptosis and long-term potentiation support the idea that these neuronal plasticity-related physiological mechanisms are essential in music⁴⁴. Cognitive functions like learning and memory require CDK5 regulation in the brain⁴⁵, thus the enrichment of CDK5 signaling pathway-related genes in our study may explain the molecular basis of these cognitive processes involved in musical abilities. In songbird studies, MEK, which is a part of CDK5 signaling pathway (Supplementary Fig. S3), is necessary for song learning⁴⁶. However, the CDK5 signaling pathway includes only a few genes identified in human studies of musical traits. The use of animal models for the study of musical traits enables the detection of this kind of brain-specific pathways that cannot be directly shown with human expression studies, limited by inaccessible of brain tissue.

Although it has been suggested that genes like *EGR1* may relate to complex social structures and social communication instead of plain auditory stimuli in songbirds^{47,48}, it may relate partially to both, speech and music. In human studies, it has been shown that musically trained individuals perform better in speech discrimination⁴⁹. Also, *FOXP2* related genetic mutation has been found in a family with language and rhythm impairment^{50,51}. Thus, partially similar features and genes are needed in music and in speech.

In the CE analysis, we included all the identified molecular studies in animals and humans related to music, including singing, music playing and listening, musical abilities and vocal learning-related traits. The analysis highly ranked those genes, which showed evidence from multiple studies. The chosen layering ensured sensitivity for molecules, whereas specificity for musical traits was less prioritized because of the phenotypic heterogeneity. However, the combination of all these studies with varying phenotypes may reveal genes that are shared between most music-related traits. Furthermore, CE analysis has potential to be utilized in other amorphous phenotypes like ADHD and autism spectrum disorders where subphenotypes may share some part of the genetic background.

The genetic predisposition for musical abilities is partially shared with general cognition^{2,52}, which was also evident by the enrichment of cognition-related genes among the top candidate genes in this study. As the cognitive capacities in humans have undergone rapid evolution, the musical abilities -related genes or pathways might have also evolved more in humans than in other animals. Thus, there can be human-specific pathways and genes affecting musical abilities not captured by analyses in this work. For example, pathways not present in mice have been shown to be important in Alzheimer disease⁵³. Study designs differ between humans and other animals: The human expression studies have concentrated on the postponed effects of music listening and practicing in the peripheral blood, whereas the animal expression studies have mostly focused on the effects of sounds and singing directly in brain tissue. Similarly, DNA-level evidence on musical abilities was only obtained from humans. Hence, this study focuses on shared genetic pathways of musical abilities and music stimuli between animal species, while the special characteristics related to specific phenotypes will remain unresolved. The phenotypic classes that were analysed separately showed some differences in the enrichment analyses especially for the ability-related genes. The difference can be largely explained by the hormones that have been mostly studied with stimuli. Although, the ability-related genes showed least functional similarities; Most of the detected functions included only few genes. However, with the limited number of studies available in each class (Table 1) the identified differences may not be true. For instance, most of the top molecules showed evidence from all three phenotype classes and the most enriched functions were almost all detected in each of the phenotype classes.

An obvious direction for future studies is to carry out phylogenetic analyses of the genes prioritized here: is there evolutionarily long-term conservation of the genes, or rather, convergent evolution? Also, it would be of interest to study the more specific role of the genes pinpointed: are some of them more related to the development of the brain, and some to the present function, as in reacting to vocal stimuli? The study was performed to elucidate key genes and novel pathways for music-related traits. The identified networks and pathways can guide future studies on genetic predisposition for music. Moreover, the gathered molecular information can be used to prioritize results in future studies considering music.

Methods

Study material. We collected studies related to music, which reported either genes or biomarkers. These included for example genetic linkage and association studies, expression and knockdown studies. The phenotypes in human studies included musical ability, absolute pitch, music listening, singing and playing instruments. In animal model studies the phenotypes were related for example to music and song exposure, vocal learning, singing and vocalization. Common denominators in the variable phenotypes were music perception and practise. The animal studies were searches to look for phenotypes that model these abilities.

The articles were collected with extensive searches through Google Scholar (<https://scholar.google.fi>), PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and Web of Science (<http://apps.webofknowledge.com>). We also searched articles from the references of the included studies and related reviews. The searched phenotypes were restricted to: music (listening, exposure, memory, aptitude, abilities, cognition, creativity, improvisation, composition or making), singing, playing instruments; vocalization, vocal/auditory phenotypes (learning, memory, plasticity, processing, perception, stimulation, imitation, improvisation or behaviour), absolute pitch, amusia, song (listening, exposure, memory, producing, complexity or variability) or musicians. Furthermore, articles with phenotypes restricted to speech (or speech-related characteristics) or considering any sounds were excluded; for example, not all studies considering singing were chosen. Additionally, we searched for studies about vocal/song control system but they were only included if suitable phenotype was used. Based on the titles and abstracts, we chose a list of 331 studies that were further examined for relevance. Studies were excluded if the phenotype was not relevant to music, if there were no significant gene or biomarker-related results reported, or if there was a similar work from the same group already included (e.g. replicative studies from the same group with similar experimental settings). Results were extracted from a total of 105 short-listed articles using available data or by contacting the authors (Supplementary Tables S1–S3).

Data extraction. All the extracted results were linked to corresponding human homologous genes using primarily biomaRt⁵⁴ from Bioconductor. HGNC (HUGO Gene Nomenclature Committee) gene symbols were used when available⁵⁵. Human association and linkage results were mapped into hg38 reference genome through markers (Ensembl, GRCh38.p5) and the genes within the regions were extracted. The linkage regions were identified from available data using primarily the reported genomic coordinates or markers. If only cM information was found, the regions around the reported peaks (usually nearest marker reported) were translated into genomic coordinates using $1\text{ cM} = 1\text{ Mb}$ formula. The association regions were identified as $\pm 500\text{ kb}$ around the associated markers. Some associated markers did drop out from the study as no genes were identified within the boundaries. To identify the associated markers, we used the thresholds reported in the studies. When there were significant and suggestive results reported in gene mapping studies, we included both of them because the convergent evidence method benefits from the integration of a larger number of results. Additionally, the significance of the association or linkage peaks do not always correlate with the true findings: true associations do not always have most extreme p-values and linkage peak width affects the probability^{56,57}. Overall, significance thresholds reported by the original authors were used when available. From our gene mapping study, we included all association results above probability score 0.2 and linkage above 0.3³.

The human homologs for the bird and other species genes were gathered from the Ensembl BioMart data mining tool (www.ensembl.org/biomart/martview), and in the instances where they could not be accessed with BioMart, data was gathered using the Ensembl (www.ensembl.org), UniProt (www.uniprot.org), miRBase (<http://mirbase.org>, version 21), EggNOG (<http://eggnogdb.embl.de>), OrthoDB (<http://cegg.unige.ch>), BLAST (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>) and Bird Base (<http://birdbase.arizona.edu>) databases. If there were multiple homologs per gene, all of them were included. Most of the genes that were found from the database were matched successfully to human homologs. However, there were a maximum of 20% of the resulting probes in some microarray studies where no current gene information was found.

The reported proteins were translated into genes encoding them. Hormones and other biomarkers that are synthesized from other substances, like estradiol, cortisol and dopamine, were included as such. Thus, the final data included genes and biomarkers.

Convergent evidence. We used the convergent evidence method implemented in GenRank Bioconductor package (<http://bioconductor.org/packages/GenRank>) to prioritize candidate genes of musical traits. This method ranks genes by integrating gene-level data from multiple evidence layers²⁵. It is a weighted vote counting method where the rank of a gene depends upon the self-importance of each evidence layer it has been detected in and the number of evidence layers it has been detected in (Supplementary Fig. S8). With the custom scores, the algorithm calculates weighted arithmetic mean for each gene, where custom scores are weights and evidence is either 1 (detection) or 0 (not detected). The algorithm allows us to combine evidence from studies where p-values and effect sizes are unavailable and where the gene sets varies across studies.

The studies were each input as one or two layers: most studies as one layer but gene mapping studies including association and linkage results were divided into separate layers. Additionally, reanalysed transcriptome datasets in a study by Drnevich, *et al.*³² were each treated as separate layers. This resulted in 111 evidence layers from the 105 articles in the analysis.

Custom scores. We assigned differential scores to each evidence layer based upon the self-importance of each evidence layer. The self-importance of each evidence layer was determined based on three arguments: sample size, phenotype and homology conversion. These three arguments were each scored from 0.8 to 1 and multiplied to form a final score for each evidence layer. The idea behind this differential scoring strategy is to penalize those evidence layers that are limited by sample size, definition of phenotype or possible errors in homology conversion. The studies that precisely used musical traits as the phenotypes were given score 1 for the phenotype,

whereas scoring for all other related phenotypes was reduced to 0.8. Human-related studies were emphasized with full scoring for homology conversion while studies of other species were given 0.8 as the homology conversion in animal models may contain errors. Also, some genes may not be found or they may have different function. The sample sizes were given continuous scoring from 0.8 to 1 within two groups of studies: gene mapping studies and other studies (including for example protein level, hormone, gene expression and knockout studies). Within these two study groups, the sample sizes were linearly scored from the smallest (getting 0.8) to the largest (getting 1.0). Additionally, the linkage layers were given reduced scoring (score multiplied by 0.9) if there were both linkage and association included from the same study. Therefore, final scores ranged from 0.512 to 1 (see Supplementary Data).

Studies were further divided into three phenotype classes related to music listening, musical ability and music practice. These classes were also separately analysed to find possible differences between the subphenotypes.

Enrichment analyses. Enrichment analyses of biological functions were performed for the top ranked genes through the use of QIAGEN's Ingenuity Pathway Analysis (IPA, QIAGEN Redwood City, www.ingenuity.com). We performed enrichment analyses of pathways, functional classes and upstream regulators to search for enriched biological functions among the top genes. The upstream regulatory analysis searches upstream regulators whose most consistent targets (from previous literature) are best enriched in the focus molecule list (our top molecule list in this case). Fisher's exact test was used for the statistical evaluation of the enrichment.

Additionally, interaction network analysis was performed to study interconnectivity between the top genes. IPA network generation algorithm searches for subnetworks with maximum interconnectivity from the global molecular network in the Ingenuity database. It starts by selecting the most interconnected focus molecules (focus molecules are here our top ranked molecules) by counting the number of connective triangles that contain the molecule. The method constructs the network around these seeds by adding more interconnected molecules until the maximum network size is reached (here, it was set to 35 molecules). The added molecules are primarily chosen from the focus molecule list, but also molecules combining many of the focus molecules can be added.

We chose top 40 molecules for these analyses. These genes are included in the top 0.995 quantile of the CE score distribution. This somewhat conservative threshold was chosen to differentiate signal from noise and include the top candidate genes which are most likely reproducible. The same quantile threshold was used for subphenotype analyses where it resulted in 29, 18 and 29 molecules for ability, listening and practice, respectively.

References

- Perani, D. *et al.* Functional specializations for music processing in the human newborn brain. *P. Natl. Acad. Sci. USA* **107**, 4758–4763 (2010).
- Mosing, M. A., Verweij, K. J. H., Madison, G. & Ullén, F. The genetic architecture of correlations between perceptual timing, motor timing, and intelligence. *Intelligence* **57**, 33–40 (2016).
- Oikkonen, J. *et al.* A genome-wide linkage and association study of musical aptitude identifies loci containing genes related to inner ear development and neurocognitive functions. *Mol. Psychiatr.* **20**, 275–282 (2015).
- Theusch, E. & Gitschier, J. Absolute pitch twin study and segregation analysis. *Twin Res. Hum. Genet.* **14**, 173–178 (2011).
- Trehub, S. E. Musical predispositions in infancy. *Ann. N.Y. Acad. Sci.* **930**, 1–16 (2001).
- Asher, J. E. *et al.* A whole-genome scan and fine-mapping linkage study of auditory-visual synesthesia reveals evidence of linkage to chromosomes 2q24, 5q33, 6p12, and 12p12. *Am. J. Hum. Genet.* **84**, 279–285 (2009).
- Park, H. *et al.* Comprehensive genomic analyses associate UGT8 variants with musical ability in a Mongolian population. *J. Med. Genet.* **49**, 747–752 (2012).
- Theusch, E., Basu, A. & Gitschier, J. Genome-wide study of families with absolute pitch reveals linkage to 8q24.21 and locus heterogeneity. *Am. J. Hum. Genet.* **85**, 112–119 (2009).
- Kanduri, C. *et al.* The genome-wide landscape of copy number variations in the MUSGEN study provides evidence for a founder effect in the isolated Finnish population. *Eur. J. Hum. Genet.* **21**, 1411–1416 (2013).
- Ukkola-Vuoti, L. *et al.* Genome-wide copy number variation analysis in extended families and unrelated individuals characterized for musical aptitude and creativity in music. *PLoS One* **8**, e56356 (2013).
- Kanduri, C. *et al.* The effect of music performance on the transcriptome of professional musicians. *Sci. Rep.* **5**, 9506 (2015).
- Kanduri, C. *et al.* The effect of listening to music on human transcriptome. *PeerJ* **3**, e830 (2015).
- Liu, X. *et al.* Detecting signatures of positive selection associated with musical aptitude in the human genome. *Sci. Rep.* **6**, 21198 (2016).
- Honing, H., ten Cate, C., Peretz, I. & Trehub, S. E. Without it no music: cognition, biology and evolution of musicality Introduction. *Philos. T. R. Soc. B* **370**, 5–12 (2015).
- Brown, S., Merker, B. & Wallin, N. L. An introduction to evolutionary musicology. In *Origins of Music* (eds Wallin, N., Merker, B. & Brown, S.) 3–24 (MIT Press, Cambridge, MA, 2000).
- Morley, I. A multi-disciplinary approach to the origins of music: perspectives from anthropology, archaeology, cognition and behaviour. *J. Anthropol. Sci.* **92**, 147–177 (2014).
- Rothenberg, D., Roeske, T. C., Voss, H. U., Naguib, M. & Tchernichovski, O. Investigation of musicality in birdsong. *Hear. Res.* **308**, 71–83 (2014).
- Jarvis, E. D. Learned birdsong and the neurobiology of human language. *Ann. N.Y. Acad. Sci.* **1016**, 749–777 (2004).
- Olson, C. R., Hodges, L. K. & Mello, C. V. Dynamic gene expression in the song system of zebra finches during the song learning period. *Dev. Neurobiol.* **75**, 1315–1338 (2015).
- White, E. J., Hutka, S. A., Williams, L. J. & Moreno, S. Learning, neural plasticity and sensitive periods: implications for language acquisition, music training and transfer across the lifespan. *Front. Syst. Neurosci.* **7**, 90 (2013).
- Yang, E. J., Lin, E. W. & Hensch, T. K. Critical period for acoustic preference in mice. *P. Natl. Acad. Sci. USA* **109** Suppl 2, 17213–20 (2012).
- Parker, J. *et al.* Genome-wide signatures of convergent evolution in echolocating mammals. *Nature* **502**, 228–231 (2013).
- Montealegre-Z, F., Jonsson, T., Robson-Brown, K. A., Postles, M. & Robert, D. Convergent evolution between insect and mammalian audition. *Science* **338**, 968–971 (2012).
- Le-Niculescu, H., Patel, S. D. & Niculescu, A. B. Convergent integration of animal model and human studies of bipolar disorder (manic-depressive illness). *Curr. Opin. Pharmacol.* **10**, 594–600 (2010).
- Niculescu, A. B. & Le-Niculescu, H. Convergent Functional Genomics: what we have learned and can learn about genes, pathways, and mechanisms. *Neuropsychopharmacol.* **35**, 355–356 (2010).

26. Ayalew, M. *et al.* Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. *Mol. Psychiatr.* **17**, 887–905 (2012).
27. Zukerberg, L. R. *et al.* Cables links Cdk5 and c-Abl and facilitates Cdk5 tyrosine phosphorylation, kinase upregulation, and neurite outgrowth. *Neuron* **26**, 633–646 (2000).
28. Tully, K. & Bolshakov, V. Y. Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. *Mol. Brain* **3**, 15 (2010).
29. Wada, K. *et al.* A molecular neuroethological approach for identifying and characterizing a cascade of behaviorally regulated genes. *P. Natl. Acad. Sci. USA* **103**, 15212–15217 (2006).
30. Jarvis, E. D. *et al.* Global view of the functional molecular organization of the avian cerebrum: mirror images and functional columns. *J. Comp. Neurol.* **521**, 3614–3665 (2013).
31. Avey, M. T., Kanyo, R. A., Irwin, E. L. & Sturdy, C. B. Differential effects of vocalization type, singer and listener on ZENK immediate early gene response in black-capped chickadees (*Parus atricapillus*). *Behav. Brain. Res.* **188**, 201–208 (2008).
32. Drnevich, J. *et al.* Impact of experience-dependent and -independent factors on gene expression in songbird brain. *P. Natl. Acad. Sci. USA* **109** Suppl 2, 17245–17252 (2012).
33. Jarvis, E. D., Scharff, C., Grossman, M. R., Ramos, J. A. & Nottebohm, F. For whom the bird sings: context-dependent gene expression. *Neuron* **21**, 775–788 (1998).
34. Mello, C. V., Vicario, D. S. & Clayton, D. F. Song presentation induces gene expression in the songbird forebrain. *P. Natl. Acad. Sci. USA* **89**, 6818–6822 (1992).
35. Haesler, S. *et al.* FoxP2 expression in avian vocal learners and non-learners. *J. Neurosci.* **24**, 3164–3175 (2004).
36. Haesler, S. *et al.* Incomplete and inaccurate vocal imitation after knockdown of FoxP2 in songbird basal ganglia nucleus Area X. *PLoS Biol.* **5**, e321 (2007).
37. Fisher, S. E. & Scharff, C. FOXP2 as a molecular window into speech and language. *Trends Genet.* **25**, 166–77 (2009).
38. Groszer, M. *et al.* Impaired synaptic plasticity and motor learning in mice with a point mutation implicated in human speech deficits. *Curr. Biol.* **18**, 354–362 (2008).
39. Oikkonen, J. *et al.* Creative Activities in Music - A Genome-Wide Linkage Analysis. *PLoS One* **11**, e0148679 (2016).
40. Hilliard, A. T., Miller, J. E., Fraley, E. R., Horvath, S. & White, S. A. Molecular microcircuitry underlies functional specification in a basal ganglia circuit dedicated to vocal learning. *Neuron* **73**, 537–552 (2012).
41. Meng, B., Zhu, S., Li, S., Zeng, Q. & Mei, B. Global view of the mechanisms of improved learning and memory capability in mice with music-exposure by microarray. *Brain Res. Bull.* **80**, 36–44 (2009).
42. Rauschecker, J. P. Cortical plasticity and music. *Ann. N.Y. Acad. Sci.* **930**, 330–336 (2001).
43. Schlaug, G., Norton, A., Overy, K. & Winner, E. Effects of music training on the child's brain and cognitive development. *Ann. N.Y. Acad. Sci.* **1060**, 219–230 (2005).
44. Martin, S. J., Grimwood, P. D. & Morris, R. G. Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu. Rev. Neurosci.* **23**, 649–711 (2000).
45. Shah, K. & Lahiri, D. K. Cdk5 activity in the brain - multiple paths of regulation. *J. Cell Sci.* **127**, 2391–2400 (2014).
46. London, S. E. & Clayton, D. F. Functional identification of sensory mechanisms required for developmental song learning. *Nat. Neurosci.* **11**, 579–586 (2008).
47. Schubloom, H. E. & Woolley, S. C. Variation in social relationships relates to song preferences and EGR1 expression in a female songbird. *Dev. Neurobiol.* **76**, 1029–1040 (2016).
48. Avey, M. T., Phillmore, L. S. & MacDougall-Shackleton, S. A. Immediate early gene expression following exposure to acoustic and visual components of courtship in zebra finches. *Behav. Brain. Res.* **165**, 247–253 (2005).
49. Schellenberg, E. G. Music training and speech perception: a gene-environment interaction. *Ann. N.Y. Acad. Sci.* **1337**, 170–177 (2015).
50. Alcock, K. J., Passingham, R. E., Watkins, K. & Vargha-Khadem, F. Pitch and timing abilities in inherited speech and language impairment. *Brain Lang.* **75**, 34–46 (2000).
51. Lai, C. S., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F. & Monaco, A. P. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* **413**, 519–523 (2001).
52. Mosing, M. A., Pedersen, N. L., Madison, G. & Ullen, F. Genetic pleiotropy explains associations between musical auditory discrimination and intelligence. *PLoS One* **9**, e113874 (2014).
53. Miller, J. A., Horvath, S. & Geschwind, D. H. Divergence of human and mouse brain transcriptome highlights Alzheimer disease pathways. *P. Natl. Acad. Sci. USA* **107**, 12698–12703 (2010).
54. Durinck, S., Spellman, P. T., Birney, E. & Huber, W. Mapping identifiers for the integration of genomic datasets with the R/Bioconductor package biomaRt. *Nat. Protoc.* **4**, 1184–1191 (2009).
55. Gray, K. A., Yates, B., Seal, R. L., Wright, M. W. & Bruford, E. A. Genenames.org: the HGNC resources in 2015. *Nucleic Acids Res.* **43**, D1079–1085 (2015).
56. Ott, J. & Hoh, J. Statistical approaches to gene mapping. *Am. J. Hum. Genet.* **67**, 289–294 (2000).
57. Zaykin, D. V. & Zhivotovsky, L. A. Ranks of genuine associations in whole-genome scans. *Genetics* **171**, 813–823 (2005).
58. Gregersen, P. K. *et al.* Absolute pitch exhibits phenotypic and genetic overlap with synesthesia. *Hum. Mol. Genet.* **22**, 2097–2104 (2013).

Acknowledgements

The work is supported by the Academy of Finland (#13771), the Biomedicum Helsinki Foundation, the Finnish Brain Foundation, the Finnish Concordia Fund and the University of Helsinki.

Author Contributions

J.O. participated in the design of the study, collected the material, carried out the statistical and bioinformatics data analyses and interpretation and drafted the manuscript. P.O. participated in the design of the study and drafted the manuscript. I.J. participated in the design of the study, collection of the material and drafted the manuscript. C.K. conceived the idea of the study, participated in the collection of the material, performed part of the bioinformatics analyses and drafted the manuscript. All authors reviewed the manuscript.

Additional Information

Supplementary information accompanies this paper at <http://www.nature.com/srep>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Oikkonen, J. *et al.* Convergent evidence for the molecular basis of musical traits. *Sci. Rep.* **6**, 39707; doi: 10.1038/srep39707 (2016).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

© The Author(s) 2016