

## Genomics approaches to study musical aptitude

Jaana Oikkonen and Irma Järvelä\*

Although music and other forms of art can develop in diverse directions, they are linked to the genetic profiles of populations. Hearing music is a strong environmental trigger that serves as an excellent model to study the crosstalk between genes and the environment. We propose that the ability to enjoy and practice music requires musical aptitude, which is a common and innate trait facilitating the enjoyment and practice of music. The innate drive for music can only have arisen by exposure to music, and it develops with motivation and training in musically rich environments. Recent genomic approaches have shown that the genes responsible for inner ear development, auditory pathways and neurocognitive processes may underlay musical aptitude. It is expected that genomic approaches can be applied to musical traits and will reveal new biological mechanisms that affect human evolution, brain function, and civilisation.

### Keywords:

■ cognition; environment; gene; inner ear development; music; musical aptitude

### Introduction

Music is universal to human culture. Listening to music does not require training. From the biological point of view, music is sound that is recognised by hair cells in the inner ear. These sounds are transmitted as electrical signals through the midbrain to the auditory cortex. It is notable that modern humans basically have an auditory centre that functions

identically to that of the first primates that lived millions of years ago [1]. These data suggest that there is high evolutionary conservation among species. However, it is not known what distinguishes humans from primates with regard to musical ability and what are the biological determinants underlying artistic cognitive traits.

Why is listening to and practising music so common in all societies? It is well known that music as a form of art has been well retained in human evolution. The evolutionary advantage of musical ability has been the subject of some debate [2]. It has been proposed that music has no effect on human evolution but that is rather a side effect of perceptual and cognitive mechanisms that serve other functions [3]. This is further emphasised by the suggestion that intense training of more than 10,000 hours is enough to make anyone a professional musician [4] though not necessarily of such prodigious talent as Mozart. Evidence for the biological underpinnings of music perception has been obtained from studies on animals and human newborns, using brain imaging and family and twin studies. Similarities between human and animal song have been detected using comparative studies. Both types of song contain a message or an intention that reflects an innate emotional state (a desire for communication, fear, or appealing) that is interpreted correctly even between different species [2, 5]. Music is non-verbal communication that is able to evoke emotions that are unique in their scale [6, 7]. In terms of evolution, communication via sounds is considered to be important for the survival of humans and other species.

The ability to appreciate music requires no explicit training, which suggests an inborn ability. Musical aptitude can be defined as the ability to understand and perceive rhythm, pitch, timbre, tone duration, and formal structure in music. The universality of musical behaviour and validity of common rules such as the use of octave-based scale systems and a preference for consonance over dissonance in nearly all types of music can be seen as evidence of innateness. Similar rules have arisen independently in isolated cultures and may apply to the music perception of non-human species [2]. This finding implies that the rules are manifest in brain organisation rather than in culture. Obviously, some animals (birds, whales) and humans sing and use the sound of singing for social communication.

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Department of Medical Genetics, University of Helsinki, Helsinki, Finland

### \*Corresponding author:

Irma Järvelä

E-mail: irma.jarvela@helsinki.fi

Observations in foetuses and infants have revealed that basic auditory abilities such as pitch discrimination and more complex capabilities such as melody recognition are already present in the early stages of development [8]. Infants obey the aforementioned universal rules of music. However, adults express more variable responses to music, depending on the culture in which they have grown up as children and in which they currently live [9]. This result implies the existence of an innate aptitude, which can be modified by environmental factors later in life. One fundamental question is which molecules are responsible for this aptitude.

A plethora of studies have demonstrated that listening to and/or performing music has multiple measurable effects on brain structure and function [10–14], demonstrating a biological effect. The role of genetic predisposition to the morphological and neurophysiologic changes has been discussed previously [12]. Based on neurophysiological studies, music activates the following brain reward centres: the limbic and mesolimbic structures including the nucleus accumbens, hypothalamus, subcallosal cingulate gyrus, prefrontal anterior cingulate, and hippocampus [14]. Various studies have suggested that music perception induces neuroplasticity and enhances neurogenesis [14, 15]. Listening to music has been reported to cause physiological changes in cerebral blood flow and cardiovascular and skeletal muscle function, as measured using positron emission tomography (PET) [11]. Moreover, active listening to music (perception) has been shown to increase endogenous dopamine release in the striatum [13], and associated emotional/behavioural responses may be linked to hormonal feedback [14]. Music is also used as a therapeutic tool in clinical settings [16, 17]. However, the molecular mechanisms and biological pathways mediating the effects of music in the human body have not been elucidated.

## Musical aptitude

Musical aptitude can be defined as the ability to understand and perceive rhythm, pitch, timbre, tone durations, and formal structure in music. In the present paper, musical aptitude refers to a primary capacity to recognize the aforementioned features of music in a person. Musical aptitude can develop to a skill/skills if the person concerned is exposed to music or musical training. These skills can be demonstrated as musical abilities. In genetic studies, the simple but challenging question is how to define musical aptitude as a concept in which the effect of music exposure is excluded. Human foetuses are exposed to music already before birth [18], so the task is challenging.

We have selected three practical tests to study the inheritance of musical aptitude. The tests cover only a small part of musical aptitude that represents complex cognitive function of human brain. The Karma Music Test (KMT) uses small, abstract sound patterns that are repeated to form hierarchic structures. KMT measures the recognition of melodic contour, grouping, relational pitch processing, and gestalt principles [19]. These are the same potential innate musical cognitive operations reported by Justus and Hutsler 2005 [20]. The subject's task is to detect structural changes in

these patterns including changes in the order or number of the tones (Fig. 1). Using the mismatch negativity (MMN) component of event-related brain potentials, subjects with high KMT scores detected better than subjects with low KMT scores the stimuli that were sound patterns. However, no difference was detected when pitches were used. These results support the validity of the test as a measure of auditory structuring instead of sensory differentiation [21]. There is evidence that musical training is not a necessary condition for a high score. Among the children who applied for lower level music instruction, those who obtained high KMT scores had less or no music training compared to those with lower KMT scores [22].

The Seashore battery of tests consists of six subtests that measure pitch, intensity, time, consonance, tonal memory, and rhythm [23]. The Seashore tests for pitch (SP) and for time (ST) consist of pair-wise comparisons of the physical properties of sound, and are used to measure simple sensory capacities such as the ability to detect small differences in tone pitch or length. Musical aptitude has also been defined using the pitch production accuracy test (PPA). In this test, a pitch produced by a device is reproduced by an individual after hearing it through a headset [24]. This test is based on singing, whereas the others are based on listening.

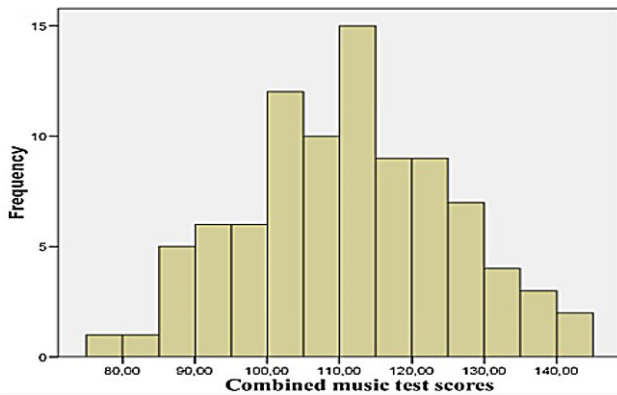
From a genetic point of view, musical aptitude varies between individuals. Musical aptitude is likely to be expressed at the population level in such a way that both extremes (extreme capacity/no capacity) are rare and the majority of individuals express moderate aptitude (Fig. 2) [25]. This is a typical feature of a complex trait attributable to several underlying genes, and it is influenced to varying degrees by environmental factors and their interactions.

## Musical traits are heritable

It has been observed that musicianship clusters in families. The amount of this aggregation that is due to genetic or cultural (i.e. environmental) factors is debatable [2]. There are several family and twin studies on music phenotypes where



**Figure 1.** The Karma Music test also called auditory structuring ability test. Three examples out of a total of 40 items belonging to the KMT (one line each). The reference pattern is repeated three times and is followed after a short pause by a test pattern that is played only once. The task is to determine whether the test pattern is the same as the three reference patterns heard first. The example in the second line has the same pattern as the reference pattern, and the other two are different.



**Figure 2.** Musical aptitude is normally distributed in a population. Musical aptitude was defined as one variable, a combined music test score (shown on X-axis) that was computed as the sum of the three test scores, Karma Music Test (maximum score 40), Seashore's test for pitch (SP) (maximum score 50), and for time (ST) (maximum score 50) in 90 subjects with less than two years of formal music education. The frequency of the scores is shown on Y-axis. The results suggest that moderate musical aptitude is common and does not need formal training.

heritability analyses have supported a genetic contribution to music perception. Heritability is defined as the proportion of the total variance of the phenotype that is genetic ( $h^2 = VG/VP$ , where VG is genetic variance and VP is the overall variance of the phenotype). In a twin study using a distorted tunes test (DTT) (the subjects' task was to recognize wrong tones incorporated into simple popular melodies) the correlation between the test scores was 0.67 in monozygous and 0.44 in dizygous twins [26]. The heritability of the auditory structuring ability test (KMT) is 0.46 in the Finnish families examined [27]. Carl Seashore's subtests of pitch (SP) and time discrimination (ST) measure the ability to detect small differences between two sequentially presented tones. The heritability scores are 0.68 and 0.21 for SP and ST, respectively. The heritability of combined KMT, SP, and ST scores COMB was 0.60 [27]. The COMB was computed as the sum of the three individual test scores after the KMT music score was scaled to the same range as the other music scores (from 25 to 50 points). The heritability of pitch perception test (PPA) that is based on singing was 40% [24]. A genetic component has also been demonstrated in rare music phenotypes such as congenital amusia and absolute pitch (AP). Congenital amusia is often referred to as "tone deafness" and is a disorder in which a subject's ability to perceive or produce music is disturbed [28]. A recent family aggregation study showed that the sibling relative risk ( $\lambda_S$ ) was estimated to be 10.8, which suggests a genetic contribution to the trait [29]. Another extreme trait is AP. AP refers to the ability to identify and name pitches without a reference pitch, and the sibling relative risk ( $\lambda_S$ ) has been estimated to range from 7.8 to 15.1 [30]. Collectively, these studies suggest that music perception is partially genetically determined. Obviously, music perception belongs to a class of human cognitive abilities that has been shown to be highly familial [31, 32].

## Genomic approaches are versatile tools to analyse musical aptitude

Current methods for analysing the human genome have revolutionised the practice of biological research. Genome-wide analyses can be applied to study human traits based on their molecular properties rather than anatomic regions. The greatest benefit of genomics is that it enables us to study biological phenomena in an unbiased and hypothesis-free fashion, without any knowledge of the biological background of the phenotype. The success of genomics has been demonstrated in medical research, where thousands of genes that cause inherited diseases or predisposition to multifactorial disorders [33] have been identified. In contrast, less attention has been paid to normal human traits.

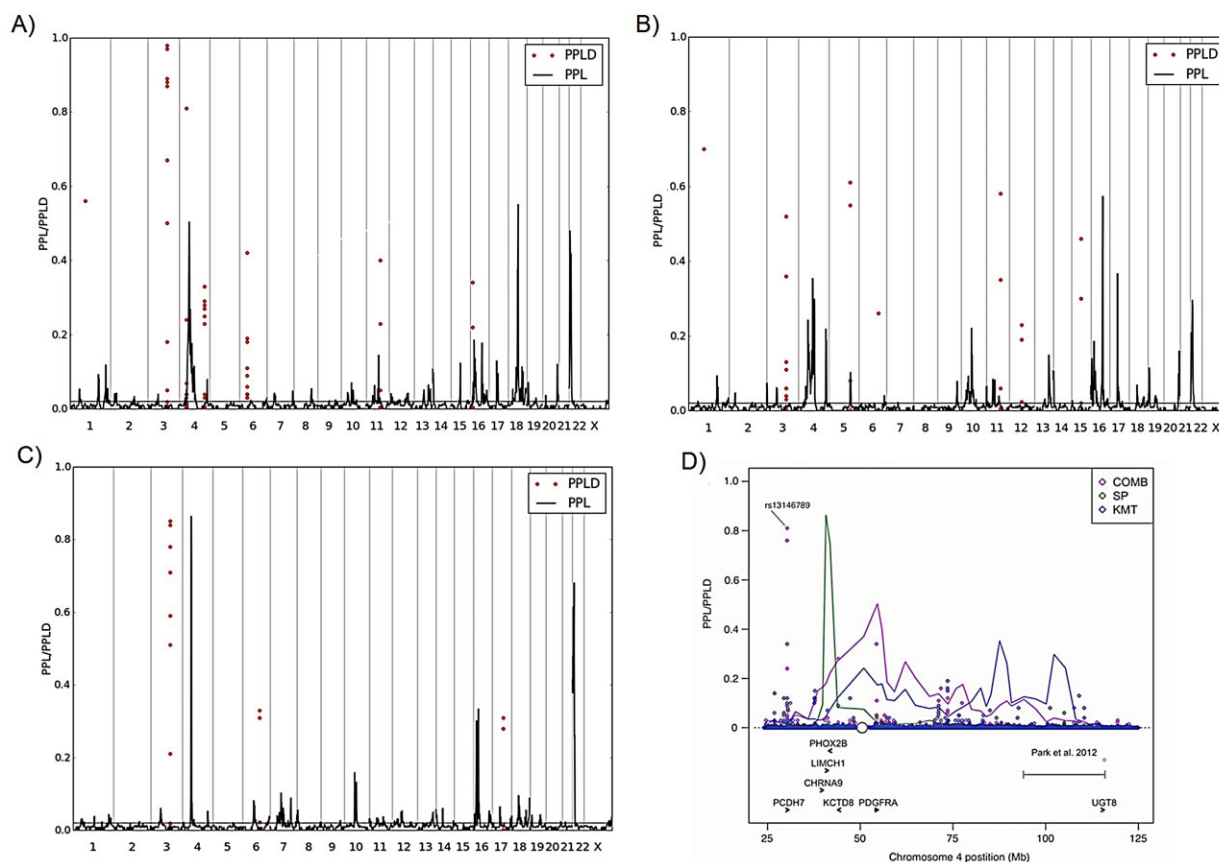
Based on Mendelian rules, children inherit half of their genes from their mother and half from their father. This is the unique strength of DNA studies in the identification of genetic variants and the reliable part of the study. The definition of the phenotype is the most challenging part of designing any study concerning the genetic background of musical ability. Most of the early studies measuring musical aptitude have been based on the subjects' abilities to perform music (for example, singing, playing an instrument, or composing music) or success in music studies [34, 35]. The ability to perform usually requires exposure to music and training in addition to several other factors such as motivation, motor skills, and memory that may also be partially inherited. Thus, the studies do not measure innate aptitude to perceive music.

Lessons from medical genetics have taught us that genetically determined traits are usually expressed early in life. The ability to learn music has been linked to a sensitivity period such as that found in language learning [36]. We hypothesise that this phenomenon is linked to brain maturation and developmentally regulated gene expression [33]. Thus, a test that can detect the early perception abilities with minimal exposure or without active training would be ideal.

Three approaches that have been used to study musical aptitude using molecular genetics methods are described in the next section.

## Genome-wide linkage and association analyses

Several genetic loci associated with musical aptitude have been identified in genome-wide linkage studies, that aim to find genetic variants that due to their proximity are inherited together with the musical aptitude [24, 27, 37]. The results suggest that musical aptitude is an innate ability that is associated with several predisposing genetic variants. Intriguingly, the genome-wide analyses performed in Finnish and Mongolian populations with different music phenotypes (KMT, SP, COMB, PPA) and different linkage mapping methods both identified a partly overlapping genetic region on chromosome 4q (Fig. 3D). The identified loci contained candidate genes that affect inner ear development and neurocognitive processes, which are necessary traits for



**Figure 3.** Genome-wide association and linkage results for musical aptitude. The results of COMB-, KMT-, and SP-scores as the phenotype are shown in **A-C**, respectively [27]. Human chromosomes are shown on X-axis (**A-C**). The linkage and association results are based on posterior probability of linkage (PPL) and posterior probability of linkage disequilibrium (PPLD) statistics and calculated on a probability scale from 0 to 1, which is interpreted directly as the probability of a trait gene being linked to/associated with the location/marker examined. The nearest genes to the associated SNPs were identified according to UCSC-database (www.ucsc.com). LD analysis using PLINK 1.07 was used to study if the associated SNPs were genetically near the genes. The best linkage was obtained on chromosome 4 for SP (**C**). **D**: Enlargement of the 4p15-q26 region of chromosome 4 and the location of the functionally relevant candidate genes. The studied SNPs are marked with open diamonds. The colours indicate different phenotypes: COMB, purple; SP, green; and KMT, blue. The best linkage region in Mongolian families [24] is shown using a grey line.

music perception. Six such candidate genes were found at chromosome 4 (Fig. 3D). The highest probability of linkage was obtained for pitch perception accuracy (SP) next to the *protocadherin 7* gene (*PCHD7*). *PCHD7* is known to be expressed in the cochlear [38] and amygdaloid [39] complexes. *PCHD7* is a relevant candidate gene for musical aptitude as the hair cells in the cochlea recognize pitches whereas the amygdala is the emotional centre of the human brain, that is affected by music, as shown in neurophysiological studies [14, 40]. Interestingly, the homologous gene *PCDH15* also affects hair cell sensory transduction [41] and causes deafness [42]. *Platelet-derived growth factor receptor alpha polypeptide* (*PDGFRA*) is expressed in the hippocampus [43] and cochlea [44] in mice. Hippocampal activity is associated with learning, memory, and with music-evoked emotions that are relevant skills for musical

aptitude [14]. *Potassium channel tetramerisation domain containing 8* (*KCTD8*) is expressed in the spiral ganglion of the cochlea. *KCTD8* also interacts with the *GABA receptors GABRB1* and *GABRB2* found within the same region [45]. *GABRB1* mRNA is strongly expressed in the hippocampus, amygdala and cerebellar granular cells in rat. In humans, *GABRB1* protein is reduced in schizophrenia, bipolar disorder, and major depression, diseases that severely affect human cognition and mood regulation [46]. *Cholinergic receptor, nicotinic alpha 9 (neuronal)* (*CHRNA9*) [47] and the *paired-like homeobox 2b* (*PHOX2B*) [48] on chromosome 4 also affect inner ear development. In addition, *PHOX2B* increase amygdala activity and autonomic functions (blood pressure, heart rate, and respiration) that are reported to be affected by music [11].

A genome-wide association approach using unrelated subjects found a strong association upstream of *GATA2 binding protein 2* (*GATA2*) at 3q21.3. *GATA2* is an important transcription factor involved in the development of cochlear hair cells [49] and the inferior colliculus (IC) [50], which both belong to the auditory pathway. Interestingly, *GATA2* is abundantly expressed in dopaminergic neurons [51] that release dopamine during emotional arousal to music [13] (Fig. 3).

A region of chromosome 16 contains a deafness locus [52] where there are two candidate genes, *cadherin type 5* (*CDH5*), and LOC283867. *Cadherin type 23* (*CDH23*) and *PCDH15* are

crucial as they are physically connected to each other in sensory hair cells [41], and have been reported to cause hearing loss in mice [53]. The most important candidate gene for pitch perception accuracy (PPA) found in the Mongolian families was *UDP glycosyltransferase 8 (UGT8)*. *UGT8* is expressed in brain, especially in oligodendrocytes [54]. The statistically most significant locus found in a genome-wide linkage study of AP is located at 8q24.21 [55]. No overlapping loci were identified in the aforementioned GWA studies and AP. It is clear that the music phenotypes are different and likely represent different loci.

## Genome wide copy number analyses

Copy number variations (CNVs) are structural genomic variants showing the highest variability in the human genome [56, 57]. CNVs play an important role in human brain cognitive function and in neuropsychiatric disorders [58, 59]. Our genome-wide CNV analysis used a SNP map of over 700,000 SNPs in large families and unrelated subjects tested for musical aptitude. The results showed several CNV regions (CNVRs) containing genes found in neuropsychiatric disorders such as schizophrenia, autism, ADHD, intellectual disability, learning disabilities, and dyslexia [60]. A deletion covering the *protocadherin-a gene cluster 1-9 (PCDHA 1-9)* was associated with low music test scores both in familial and sporadic cases [60]. PCDHAs affect synaptogenesis and maturation of the serotonergic projections of the neurons in most of the brain regions [61]. *Pcdha* mutant mice show abnormalities in learning and memory [62]. Another gene, *galactose mutarotase (GALM)* that affects serotonin transporter binding potential of the human thalamus [63] was identified in a duplicated genomic region in musically creative individuals. The thalamus in the midbrain is an important region for music perception [14].

## Candidate gene studies on musical aptitude and related traits

Music serves as a tool for social communication that can be transacted without language. The hormone arginine vasopressin (AVP), highly conserved in evolution, is reported to affect many social, emotional, and behavioural traits including pair bonding and altruism in humans and other species [64]. The AVP receptor 1A is coded by the *AVPR receptor 1A* gene. This receptor mediates the influence of the AVP hormone in the brain [65]. The human serotonin transporter (*5-HTT, SLC6A4*) gene and the *arginine vasopressin receptor (AVPR1A)* gene have been associated with artistic creativity in professional dancers [66] and short-term musical memory [67]. *AVPR1A* alleles (markers RS1 and RS3) showed the strongest association with KMT [68]. The results suggest that the neurobiology of music is likely related to the pathways affecting natural affection that is exemplified by mothers taking care of their newborns. The microsatellites RS1 and RS3 are located in the promoter region and have demonstrated differences in relative promoter activity with respect to allele length: the shorter alleles of RS1 decrease

*AVPR1A* transcription in the amygdala, which in turn increases the amygdala activity, leading to social withdrawal [69]. The mechanism by which the microsatellite allele length actually affects transcription efficacy is not known.

## Conclusions

Musical aptitude is common to all mankind and a prerequisite for enjoying and practising music. Exposure to music may trigger hidden musical aptitude and awaken interest towards music. Can genes explain why some people are naturally more interested in music than others? Genome-wide analyses of musical aptitude suggest that genes that affect the auditory pathway and neurocognitive functions are plausible candidate genes for musical aptitude. Many of the candidate genes are found in other species, suggesting their possible role in mammalian evolution. In fact, a wide-spread adaptive convergent sequence evolution has recently been found in echolocating bats and dolphins [70], implicating numerous genes linked to hearing, but also vision, among them protocadherin15 (*PCDH*), also found in our GWA-study [27]. The results of GWAS are probabilistic, and additional proof is needed in the form of replicate studies, candidate gene studies, and functional studies to confirm the current results. Genomics approaches are also suitable to elucidate the evolution of music. There are variations in music test scores in our material that suggest that the alleles may have been targeted for selection. Alleles under positive selection increase in prevalence in a population, leaving “signatures” or patterns of genetic variation on the DNA sequence. Recent studies on mitochondrial DNA variation in indigenous Taiwanese populations showed significant correlation with music culture (using traditional folk-songs). These correlations were stronger than those found with genes and languages and with music and languages with regard to population structure and suggest that music and genes may have co-evolved [71, 72]. Thus, musical practices may be tightly linked to human genetic profiles and have the potential to serve as a marker of human history. The findings provide a valuable background for molecular studies and research on the interplay between genes and the environment with respect to auditory perception and its evolution.

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