Music has existed throughout the history of man. There is an abundance of data available about the neurophysiological effects of music on the human brain, but heritability of music and especially molecular studies have been lacking. This is the world's first molecular genetics thesis concerning musical aptitude and related traits. This thesis aimed to investigate the genetic background of music perception and related phenotypes in Finnish pedigrees. These include creative functions in music and listening to music. The results suggest that both musical aptitude and creative functions in music have strong genetic components. The findings suggest that musical aptitude and creative functions in music are likely to be regulated by several predisposing genes or variants. Based on the results obtained in this study, creative functions in music are affected by different predisposing genetic variants than musical aptitude.

ISBN 978-952-10-8786-8 (paperback)
ISBN 978-952-10-8787-5 (PDF)

LIISA UKKOLA-VUOTI SEARCH FOR GENETIC VARIANTS UNDERLYING MUSICAL APTITUDE AND RELATED TRAITS

UNIVERSITY OF HELSINKI
FACULTY OF MEDICINE



LIISA
UKKOLA-VUOTI

Search for Genetic Variants Underlying Musical Aptitude and Related Traits

HELSINKI 2013

SEARCH FOR GENETIC VARIANTS UNDERLYING MUSICAL APTITUDE AND RELATED TRAITS

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Academic dissertation

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in the lecture hall 3 of Biomedicum Helsinki I, Haartmaninkatu 8, Helsinki,
on May 10th 2013, at 13 noon.

Helsinki 2013

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ISBN 978-952-10-8786-8 (paperback)
ISBN 978-952-10-8787-5 (PDF)
http://ethesis.helsinki.fi/

Cover art: Liisa Ukkola-Vuoti, MusicGene, collage, 2013
Cover layout: Riikka Hyypiä

Unigrafia, Helsinki 2013

To my family

Väritän värityskirjaa
vedän viivan pisteestä toiseen
kokoan palapeliä
josta puuttuu paloja
joku auttaa löytämään
toinen katkoo kyniä
väritän värityskirjaa
aikamyrskyssä

Ismo Alanko

I paint the colors on the empty paper
I draw the lines from dot to dot
I am assembling a puzzle
with missing pieces
One is helping me to discover
One is breaking my pencils
I am painting a picture inside a storm of changes

Translated by Sauli Vuoti

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I **Ukkola LT**, Onkamo P, Raijas P, Karma K, Järvelä I (2009) Musical aptitude is Associated with *AVPR1A*-Haplotypes. PLosOne, 4(5):e5534.

II **Ukkola-Vuoti L**, Oikkonen J, Onkamo P, Kama K, Raijas P, Järvelä I (2011) Association of the arginine vasopressin receptor 1A (*AVPR1A*) haplotypes with listening to music. J Hum Genet 56; 324-329.

III **Ukkola-Vuoti L***, Kanduri C*, Oikkonen J, Buck G, Blancher C, Raijas P, Karma K, Lähdesmäki H, Järvelä I (2013) Genome-wide copy number variation analysis in extended families and unrelated individuals characterized for musical aptitude and creativity in music. PLosOne, PLoS ONE 8(2): e56356.

IV **Ukkola-Vuoti L**, Oikkonen J, Onkamo P, Raijas P, Karma K, Järvelä I (2012) Genome-wide association analysis show evidence for *PRKG1* gene in creative functions in music in Finnish families. Manuscript.

*Equal contribution

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The author's main contributions to the papers are:

Publication I Conceived and designed the experiments, collected the data from the background information questionnaire, performed the laboratory experiments (genotyping), participated in the data analysis (FBAT, QTDT and SPSS), designed the tables and the figures for the manuscript, and drafted the manuscript.

Publication II Conceived and designed the experiments, collected the data from the background information questionnaire, performed the laboratory experiments (genotyping), participated in the data analysis, designed the tables and the figures for the manuscript, and drafted the manuscript.

Publication III Participated in the collection of the study samples and testing of participants musical aptitude, collected and analyzed the data from the background information questionnaire, extracted DNA, send the samples for genotyping, analysis of the gene lists obtained from CNV-regions, designed the tables and the figures for the manuscript, and wrote the paper with the help of C Kanduri and I Järvelä

Publication IV Participated in the collection of the study samples and testing of participants' musical aptitude, collected and analyzed the data from the background information questionnaire, extracted DNA, send the samples for genotyping, analysis of the gene lists, designed the tables and the figures for the manuscript, and wrote the paper together with the supervisors.

ABBREVIATIONS

5-HTT	serotonin transporter
5-HTTLPR	serotonin-transporter-linked polymorphic region
ACAP1	ArfGAP with coiled-coil, ankyrin repeat and the PH domains 1 gene
ALPK1	alpha-kinase 1
AP	absolute pitch
AVP	arginine vasopressin
AVPR1A	arginine vasopressin receptor type 1A gene
bp	base pair
CNV	Copy Number Variation
CNVR	Copy Number Variable Region
COMB	combined music test scores
COMT	catechol-O-methyltransferase gene
DA	dopamine
DNA	deoxyribonucleic acid
DRD2	dopamine receptor D2 gene
DTT	distorted tunes test
EEG	electroencephalography
ELOVL6	ELOVL fatty acid elongase 6
FBAT	family-based association test
fMRI	functional magnetic resonance imaging
GxE	gene-environment interactions
GALM	glucose mutarotase gene
GWAS	genome wide association study
GWS	genome wide study
h^2	heritability
IQ	intelligence quotient
kb	kilobase

KMT	Karma music test
LD	linkage disequilibrium
LOD	logarithm of odds
Mb	megabase
MCTP2	multiple C2 domains, transmembrane 2 gene
MEG	magnetoencephalography
MMN	mismatch negativity
MRI	magnetic resonance imaging
NAc	nucleus accumbens
PCDHA	protocadherin-α gene cluster
PCR	polymerase chain reaction
PET	positron emission tomography
PLSCR3	phospholipid scramblase 3gene
PPA	pitch production accuracy test
POLR2A	RNA polymerase II polypeptide A gene
PRKG1	cGMP-dependent protein kinase type I gene
RASGRF2	Ras protein-specific guanine nucleotide-releasing factor 2 gene
SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4
SNP	single-nucleotide polymorphism
SP	Seashore pitch discrimination subtest
ST	Seashore time discrimination subtest
TPH1	tryptophan hydroxylase gene 1
UGT8	UDP glycosyltransferase 8
VNTR	variable number tandem repeats

ABSTRACT

Music perception and practice represents complex cognitive functions of the brain. There is an abundance of data about the neurophysiological effects of music on the human brain, but heritability and especially molecular studies have been lacking. The development of genome technologies and bioinformatics has enabled the identification of genetic variants underlying complex human traits. These methods can be applied to normal human traits like music perception and performance.

Prior to this study, the first genome wide scan in the Finnish pedigrees suggested that musical aptitude is associated with several chromosomal areas in the human genome. High heritability of music test scores was also demonstrated. In order to further dissect the molecular genetic background of music related traits this thesis work focused on three phenotypes in music, musical aptitude, listening to music and creativity in music in the enlarged family material. For the aforementioned phenotypes functionally relevant candidate genes were analyzed (I-II), and novel genomic variants and candidate genes sought using genome-wide analysis of single nucleotide polymorphisms (IV) and structural variation (copy number variation; CNV) (III).

In this thesis, musical aptitude of each participant was defined using three music tests: the auditory structuring ability test (Karma Music test) and Seashore's pitch and time discrimination subtests. A combined music test score (COMB) was computed as the sum of the separate scores of the three individual test results. Information about other musical traits, creative functions in music and listening to music, and background information was collected using a web-based questionnaire.

Both musical aptitude and creative functions in music showed to have strong genetic components, the heritability estimates were 0.44 and 0.84 respectively (I). On the average, the amount of time spent on active listening to music was 4.6 hours per week and passive 7.3 hours per week (II) among the participants. Furthermore, high scores in music tests correlated with creative functions in music, and high amount of active listening to music correlated with the high level of music education (I-II).

Five candidate genes, *AVPR1A*, *SLC6A4*, *COMT*, *DRD2* and *TPH1*, were studied in musical aptitude, creativity in music and listening to music. All studied traits were associated with the arginine vasopressin receptor 1A (*AVPR1A*) gene, suggesting that the neurobiology of music perception and practice is likely to be related to pathways affecting social affiliation and communication (I-II).

In the genome-wide CNV study several copy number variable regions containing genes that affect neurodevelopment, learning and memory were detected. The most promising of them was a deletion at 5q31.1 covering the protocadherin-α gene cluster (*PCDHA*) that was associated with low music test scores. *PCDHA* is involved in neural migration, differentiation and synaptogenesis. Creativity in music was associated with a duplication covering glucose mutarotase gene *(GALM)* at 2p22. A 1.3 Mb duplication was identified in a subject with low COMB scores overlapping the core linkage region of absolute pitch at 8q24 (III).

Genome-wide association analysis of creative functions in music showed association with several genes previously shown to be related to learning, memory, synaptic plasticity and neuropsychiatric disorders. The strongest association was detected with the cGMP-dependent protein kinase type I (*PRKG1*) gene at 10p21 that affects amygdala function, a brain area also induced by music. *PRKG1* has previously been associated with schizophrenia and attention deficit hyperactivity disorder (IV).

In conclusion, our results suggest new candidate genes for musical aptitude and creativity in music. Being aware that musical aptitude is a complex phenotype affected by several predisposing alleles, this result, although interesting, is preliminary and may only partially explain the genetic background of musical aptitude. Further studies are needed to confirm the role of the candidate genes identified in musical aptitude and related traits.

TIIVISTELMÄ

Ihmiset eroavat musikaalisilta taipumuksiltaan ja musikaalisuus ilmenee monin eri tavoin. Monet tunnetut ilmiöt, kuten musiikin ihmelapset, musikaaliset kaksoset tai sisarukset, antavat viitteitä musiikin ja biologian läheisestä yhteydestä. Silti musikaalisuuden periytyvyyden ja erityisesti sen taustalla olevan molekyylibiologian tutkiminen on käynnistynyt vasta viime vuosina. Geneettisten tutkimusmenetelmien kehittyminen on luonut uusia työkaluja ja mahdollistanut monitekijäisten ominaisuuksien, kuten musikaalisuuden taustalla vaikuttavien geneettisten muutosten etsimisen.

Ensimmäinen musikaalisuuden koko perimän kattava kartoitus suoritettiin suomalaisissa suvuissa. Tutkimus osoitti perimän usean eri alueen vaikuttavan musikaalisuuteen. Tämän väitöskirjan tarkoituksena on selvittää tarkemmin musikaalisuuden, musiikin kuuntelemisen ja musiikillisen luovuuden molekyyligeneettistä taustaa edellisestä tutkimusta laajemmassa perhemateriaalissa. Tutkimuksessa analysoitiin toimintansa perusteella merkityksellisiä ehdokasgeenejä (I-II). Lisäksi koko perimän kattavissa tutkimuksissa etsittiin uusia musikaalisuuteen ja musiikilliseen luovuuteen vaikuttavia perimän muutoksia ja ehdokasgeenejä yhden nukleotidin geenimerkkejä (IV) sekä kopiolukumuutoksia (CNV) (III) käyttäen.

Tutkimushenkilöiden musikaalisuus määritettiin kolmea musikaalisuustestiä käyttäen: auditiivisen strukturointikyvyn testi (Karman testi) sekä Seashoren äänen korkeuden ja keston testit. Näiden kolmen musikaalisuustestin pistemäärän summana laskettiin kunkin osallistujan yhdistetyt musikaalisuuspisteet (COMB). Osallistujien musiikki- sekä muusta taustasta kerättiin tietoa laajalla Internet-pohjaisella kyselylomakkeella.

Havaitsimme musikaalisuuden ja musiikillisen luovuuden perinnöllisen komponentin olevan merkittävä, musikaalisuuden 44 % ja musiikillisen luovuuden 84 % (I). Tutkimukseen osallistuneet kuuntelivat musiikkia aktiivisesti keskimäärin 4.6 tuntia viikossa ja passiivisesti 7.3 tuntia viikossa (II). Lisäksi korkeat musikaalisuustestipisteet korreloivat musiikillisen luovuuden kanssa ja aktiivinen musiikin kuunteleminen musiikkikoulutuksen kanssa (I-II).

Tutkimme viiden ehdokasgeenin, *AVPR1A, SLC6A4*, *COMT*, *DRD2* ja *TPH1*, vaikutusta musikaalisuuteen, musiikilliseen luovuuteen ja musiikin kuuntelemiseen. Havaitsimme, että kaikki tutkitut ominaisuudet liittyivät *AVPR1A* geeniin (I-II). Koska *AVPR1A*-geeni on aikaisemmissa tutkimuksissa liitetty sosiaaliseen kommunikaatioon ja kiintymykseen, tuloksemme viittaavat, että musiikin aistimisen ja tuottamisen neurobiologia liittyy samoihin biologisiin reitteihin.

Koko perimän kattavassa CNV -työssä havaitsimme kopioluvultaan vaihtelevia alueita, jotka sisälsivät hermosolujen kehittymiseen, oppimiseen ja muistiin liittyviä geenejä. Mielenkiintoista oli, että *PCDHA* geeniperheen poistuma kromosomissa 5q31.1 liittyi mataliin musiikkitestipisteisiin. Aikaisemmin *PCDHA* on liitetty hermosolujen migraatioon, erilaistumiseen ja synapsien muodostumiseen. Havaitsimme musiikillisen luovuuden liittyvän *GALM* geenin kahdentumaan kromosomissa 2p22. Lisäksi löysimme matalat COMB pisteet omaavalta henkilöltä suuren, 1.3 Mb, kahdentuman kromosomista 8q24 absoluuttiseen sävelkorvaan kytkeytyvältä alueelta (III). Etsiessämme musiikilliseen luovuuteen liittyviä geenejä, havaitsimme useita oppimiseen, muistiin, hermosoluliitosten muovautumiseen ja neuropsykiatrisiin sairauksiin liitettyjä geenejä. Näistä mantelitumakkeen toimintaan vaikuttava *PRKG1* –geeni assosioitui voimakkaimmin musiikilliseen luovuuteen (IV).

Tähänastiset tutkimukset osoittavat, että musikaalisuus on monitekijäinen ominaisuus, mihin vaikuttavat ympäristön lisäksi useat altistavat geenimuodot. Löydöksemme ovat alustavia eivätkä yksinään riitä selittämään musikaalisuuden perinnöllistä taustaa. Uusien ehdokasgeenien tunnistaminen musikaalisuudessa ja musiikillisessa luovuudessa tulee antamaan lisätietoa musikaalisuuden biologisesta taustasta.

1. INTRODUCTION

Music is an ancient and universal trait that has existed through the history of man. Music's ability to establish attachment between individuals is evident; lullabies attach infant to a parent and singing or playing music together adds group cohesion (Insel & Young 2001; Peretz 2006). The similarity between animal and human song as well as between ancient and new music supports the idea that music is coded in our genes. The neuronal architecture of an infant is ready to process music already at birth (Zentner & Kagan 1996; Perani et al. 2010) and multiple measurable effects of listening to and/or playing music on brain structure and function further suggest a biological effect of music. Music has been shown to activate specific areas, e.g. cortical regions, hippocampus, thalamus and amygdala of the brain (Bengtsson et al., 2007; Berkowitz & Ansari 2008; Limb & Braun 2008; de Manzano & Ullen 2012; Liu et al. 2012). Listening to music activates mesolimbic structures including the nucleus accumbens and the hypothalamus, the reward centers of the brain (Menon & Levitin 2005), but molecules mediating these effects remain so far uncharacterized.

Musical aptitude manifests itself in many different ways. For example, a person may have ability to detect small differences in tone pitch or duration, the structures of music, or the ability to intuitively learn or appreciate music. Musical aptitude is varying between individuals so that the most of us have moderate ability whereas less or more capable individuals are less common (Karma 2007). Different test patterns have been developed to measure individuals' musical aptitude (Seashore 1960; Shutter-Dyson & Gabriel 1981; Karma 2007). The tests have been used e.g. to define musical abilities of children applying in music schools.

Recent studies have revealed a substantial genetic component in music perception including absolute pitch (Theusch et al. 2009), congenital amusia (Peretz et al. 2007), auditory structuring ability (Pulli et al. 2008) and musical ability (Park et al. 2012). The heritability of musical aptitude or ability was estimated to be 40-48 % (Pulli et al. 2008; Park et al. 2012). Genome-wide analyses and candidate gene studies in musical traits have suggested such candidate genes as *AVPR1A, SLC6A4, UNC5C* and *UGT8* for musical abilities (Granot et al. 2007; Pulli et al. 2008; Morley et al. 2012; Park et al. 2012). These preliminary molecular

studies support the hypothesis that musical aptitude is a complex trait resulting from currently unknown number of genomic variations, environment, and their complex interactions.

The definition of creativity is that it is an ability to produce work that is both original and appropriate for the situation in which it occurs (Sternberg & Lubart 2006). Creativity requires the simultaneous presence of several traits, e.g. intelligence, perseverance, divergent thinking and unconventionality (Csikszentmihályi 1990; Csikszentmilhályi & Wolfe 2000; Bachner-Melman 2005). Several lines of evidence for genetic effect for creativity have been published (Waller et al. 1993; Bachner-Melman et al. 2005 Reuter et al. 2006; Keri 2009; Kyaga et al. 2011). Creativity in music is the prerequisite of music culture and industry. Composing, arranging and improvising music are high-level creative functions of brain and defined as "creative functions in music" in this thesis.

The purpose of this thesis was to investigate the genetic variants underlying musical aptitude, listening to music and creative functions in music in Finnish pedigrees. This is the first molecular genetic thesis in the world concerning musical aptitude and related traits. It is important to know what the normal functions of the brain are and what the molecules behind these functions are. Obviously, the results presented in this thesis also have immediate relevance also to studies focusing on diseases.

2. REVIEW OF THE LITERATURE

2.1. Biological background of music

2.1.1. Evolution of music

Music, like language, has an ancient and universal character. Throughout the history of mankind, on every part of the globe, there has been music (Hauser & McDermott 2003; Peretz 2006). Obviously, the archeological evidence of human song is lacking, thus its age cannot be traced. Records of fossil instruments (Figure 1) indicate that ancient music might actually have been quite similar to the music of today (McDermott & Hauser 2004; Peretz 2006; Conrad et al. 2009; Higham et al. 2012). The construction of instruments is a sign of higher level music culture, suggesting that instrumental music has evidently existed for at least for 40,000 years (Conrad et al. 2009; Higham et al. 2012). Further, common rules and other similarities in music worldwide such as use of octave-based scale systems and preference for consonance over dissonance in nearly all types of old and new music can be seen as evidence of innateness (McDermott & Hauser 2004; Peretz 2006).

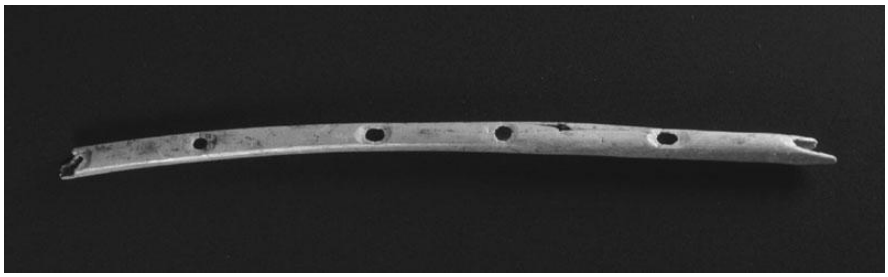


Figure 1. The earliest musical instruments were found from Germany and are 42-43,000 years old. Reprinted with permission. Conrad et al. Nature 2009.

Research for the biological basis of music has expanded since the days when Darwin first proposed (in 1871) music served to attract the opposite sex, to signal the quality of a mate, to signal territoriality and to express emotions (Fitch 2006). Evidence of protolanguage, from which language and music evolved, has been widely obtained as human social

communication. For example, lullabies are communication between parent and infant and are thought to increase attachment, while singing or playing music together can add group cohesion or coordinate coalitions (Insel & Young 2001; Hagen 2003; Peretz 2006). Music is not truly essential for survival but it nevertheless recruits some of the same brain systems associated with biologically driven essential functions like subsistence and reproduction (Zatorre et al. 2003). Further, an overlap of the behavioral and neural resources between language and music has been suggested by a number of studies (e.g. Koelsch et al. 2002; Levitin & Menon 2003; Patel 2003; Zatorre et al. 2003; Brown et al. 2006; Sammler et al. 2012; Zatorre & Baum 2012). The age of an individual when they begin studies seems to play a crucial role both in foreign language acquisition skills and in music (Johnson & Newport 1989; Marin 2009; Penhune 2011). However, it has also been proposed that music is only a side-effect, "auditory cheesecake", of various perceptual and cognitive mechanisms serving other functions and serves no adaptive function (Pinkers 1997).

Nowadays people spend a lot of time listening to or practicing music, and use substantial amounts of money to go on concerts, on records and musical instruments. Studies on musical practices show that about 50 % of the population have played or currently play an instrument (North et al. 2010), and listening to music is the most popular indoor activity in our societies (Peretz 2006; North et al. 2010). These data show that humans have a deep need to create, perform, and listen to music, all of which suggests that music, in essence, is coded in our genes.

2.1.2. Animal studies; analogies and homologies of music

Animals do not make or experience music in the same sense as human do. However, some animals, like birds, gibbons and whales, are said to sing (McDermott & Hauser 2005; McDermott 2008). Over 4,500 species of songbirds are capable of singing with remarkable diversity of tonal, structural and learning characteristics (Williams 2004), whereas capable mammalian species are far less diverse in their abilities. Basic pitch or rhythm abilities, as well as the discrimination of human music genres or styles have been studied in animals (Porter 1984; Watanabe & Sato 1999; Chase 2001; Hagmann & Cook 2010). In the study of Porter (1984) pigeons learned to discriminate between complex musical sequences (flute music by Bach from viola music by Hindemith). Further, the study of Watanabe & Sato

(1999) showed that Java sparrows were able to learn the discrimination of music genres (music by Bach and Schoenberg, as well as, by Vivaldi and Carter). Later on, Chase (2001) showed that also goldfishes learned to discriminate between musical stimuli (blues from classical music and Bach). Also, the study of auditory rhythmic discrimination of pigeons showed the capability to time periodic auditory events, but limited appearance of generalized rhythmic groupings (Hagman & Cook 2010). As shown here, music may have stimulus properties common to humans, birds, and even fish. Thus, the basic capacities for perceiving music and/or sounds similar to human are also present in the animal kingdom. The features of music perception in animals cannot be part of an adaptation for music, but must instead represent a capacity that evolved for more general auditory analysis (Hauser & McDermott 2003).

In terms of evolution music can be considered as production and perception of sounds that are important in the communication between individuals, and even between individuals from different species. It has been hypothesized that music has survived through evolution due to its tendency to bear reward and its power to evoke strong emotions. Reward and emotions help individuals to adapt to new or difficult situations (withdrawal, danger, love etc.) (Cross 2003; Gosselin et al. 2007). Based on comparative studies similarities between human and animal song have been detected: both contain a message, an intention that reflects an innate emotional state (Fitch et al. 2006). Birdsong is affected by the conditions and social context the singer experiences, and has an effect on the behavior of the listeners (Williams 2004). Similarly, emotions and social context affect performing musicians; improvising music is considered as an inter-subjective co-ordination of musical acts with other musicians or/and between a musician and the listeners. Numerous similarities found between humans and animals indicate that the trait did not evolve only for music. Usually, animal song is a result of the activation of a complex vocal organ and neural song circuits when hormone levels, for example dopamine, in male songbirds, or male whales etc. (Fitch 2005; Rauceo et al. 2008), is high during the time for reproduction (Fitch 2006).

Already Darwin noticed similarities between the human and bird “music”, and suggested that they were evolutionary analogs (Darwin 1871), that is, similar traits that have evolved independently in different lineages without common ancestors (Fitch 2006; Rauceo et al. 2008). In addition to birdsong, the song of whales (Payne & McVay 1971) can be considered

as analogous to human music. The capability for vocal learning in human and animal traits can be considered as a solution for communication between individuals (Fitch 2005 & 2006; Masataka 2007). Songbird chicklings need exposure to song to learn to sing properly. Vocal learning is critical in human language, and also relevant in musical song, supporting the analog facet (Fitch 2005 & 2006). Vocal learning, that is both learned and complex enough to be considered as song, is rare among mammals (Williams 2004; Fitch 2005 & 2006). Humans are the only primate species capable of imitating signals of vocal communication. The song of gibbons may serve a similar adaptive function to songbird or human song but seem to rely on different neural mechanisms and is complex but not learned (Fitch 2005). Considering other mammals: whales, dolphins, and two species of bats can imitate vocal signals (Williams 2004). Vocal learning bird species are more numerous and birdsong has evolved at least three times in birds (songbirds, parrots and hummingbirds) (Doupe & Kuhl 1999).

Homology is another form of similarity, where similar traits in two or more different species actually derive from a common ancestor (Fitch 2005 & 2006). Some plausible auditory perception homologies in humans and other vertebrates can be found, such as music created using instruments or other "sound tools", though this is quite rare (Fitch 2006). Although nonhuman primates do not seem to share language nor musical abilities with us (Figure 2) (McDermott & Hauser 2007), their vocal communication and drumming behaviour may be homologous to humans (Fitch 2005; Remendios et al. 2009). In the study of McDermott & Hauser (2007), non-human primates (tamarins and marmosets) were shown to prefer slow tempo music but silence was chosen if it was included as an alternative. It was suggested that homologous mechanisms for tempo perception might be found in human and nonhuman primates but motivational ties to music are uniquely human (McDermott & Hauser 2007).

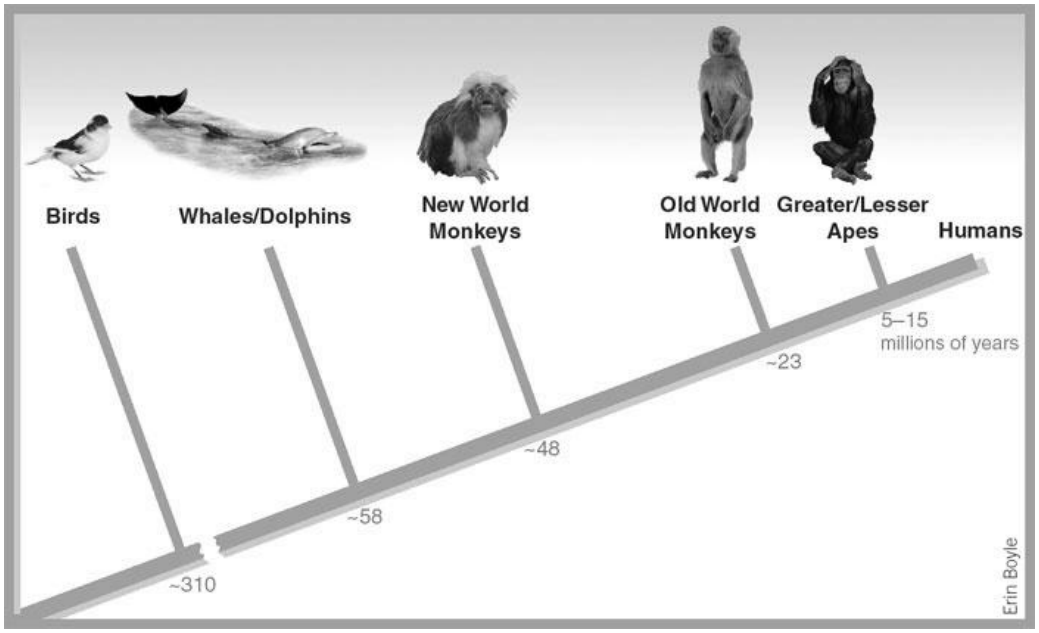


Figure 2. Phylogeny of taxonomic groups of animals used in studies of the origins and evolution of music. Divergence times based on recent molecular data are presented at the nodes. Reprinted with permission. Hauser & McDermott Nature neuroscience 2003.

2.1.3. Biological context of music and the perception of sounds

Human perception of sounds is a complex cognitive process, partly considered to be shared with other vertebrates and partly unique to our species (see chapter 2.1.2) (Chase 2001; Fitch 2005: McDermott & Hauser 2005; Masataka 2007). Music consists of sound and silence with changes in pitch, time and timbre, however, there is cultural as well as individual variation in what is considered as music. Biologically, music can be considered as production and perception of sounds that mediate communication.

Basically, music is sound waves that are travelling in the air. The perception of sounds begins in the cochlea, the auditory portion of the inner ear, where the sound waves are entering via the auricle and auditory canal of the external ear and the bones of the middle ear. In the cochlea, the auditory stimulus is transformed from mechanical stimuli into neural activity and further processed in the auditory brainstem (Figure 3). This acoustic information undergoes complex processing stages before the body reacts to it and the perception of music becomes conscious. The first processing stage in the brainstem is essential because it enables rapid

reacting to auditory signals (for example, in the case of signals indicating danger) at the level of the superior colliculus and the thalamus. Further, the thalamus projects the information into the auditory cortex where more specific information about acoustic signal, like pitch height and chroma, intensity and timbre, is extracted (Brownell 1997; Koelsch & Siebel 2005).

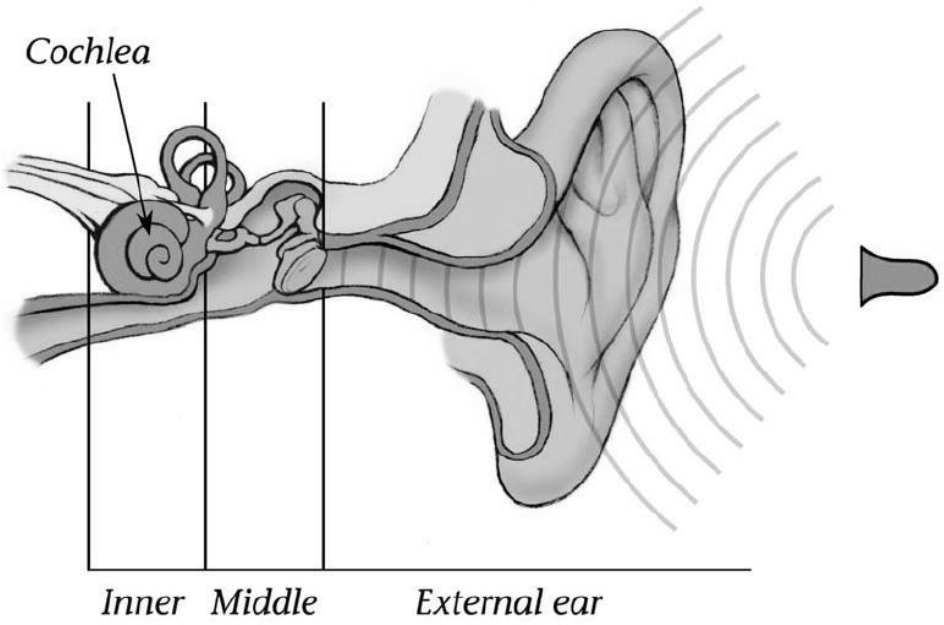


Figure 3. The sound waves come through the auricle and auditory canal of the external ear to the middle ear where the vibrating eardrum and ear bones mediate acoustic information to the cochlea of the inner ear. Sound perception begins in the cochlea and the auditory nerve carries signals to the auditory area of the brain. Reprinted with permission. Brownell The Volta revew 1997.

2.1.4. Musical aptitude

Musical aptitude manifests itself in many different ways. A person may have an ability to understand and perceive differences in pitch, rhythm, intensity, timbre, harmonies and/or the structures of music. Further, kinesthetic musical feeling and the ability to intuitively learn or appreciate music are part of musical aptitude.

Simple sensory capacities, such as the ability to detect small differences in tone pitch or duration, are necessary for musical aptitude (Figure 4) (Seashore 1960). According to the model of auditory theory, traits that we usually understand as musical abilities are secondary skills (Figure 4), while primary capacities are a prerequisite for the development of these skills (Karma 1994). The secondary musical skills are culture dependent and modified by environment while primary capacities reflect more innate musical aptitude.

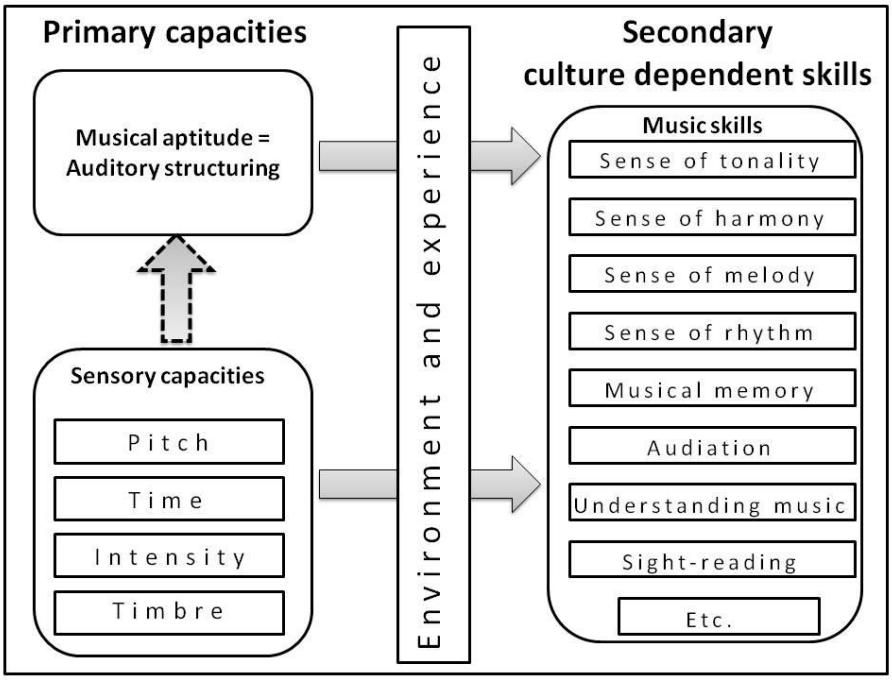


Figure 4. Model of auditory structuring. Primary capacities (left) are essential for the development of secondary music skills (right). Environment and experience have an effect on music skills. Modified from Karma 2007.

Various tests have been developed to explore an individual's musical capacity. In the following, four of them are described in detail. The Seashore battery of tests consists of six subtests that measure elementary abilities considered by the designer as important for musical aptitude (pitch, intensity, time, consonance, tonal memory, and rhythm), one at a time. Of the subtests tonal memory, intensity and pitch, respectively, have shown the highest reliabilities (0.83, 0.72 and 0.71, respectively) (Table 1) (Shutter-Dyson & Gabriel 1981). Wing's battery of seven subtests measures aural acuity as well as music taste or preference (chord analysis, pitch change, memory, rhythm, harmony, intensity and phrasing). The whole test shows good reliability of 0.91 (Table 1) (Shutter-Dyson & Gabriel 1981). Gordon's test consists of three parts: tonal imagery (melody and harmony), rhythm imagery (tempo and metre) and musical sensitivity (phrasing, balance and style). The Gordon musical aptitude profile test is the most reliable with a reliability of 0.92-0.95, but it takes three and a half hours to finish and it is recommended that it be divided over three different days (Shutter-Dyson & Gabriel 1981). The Karma music test (KMT) consists of sound patterns: according to the designer, describing musical aptitude as a sound patterning ability keeps it relatively homogenous excluding emotions or personality traits (Karma 2007).

The nature of musical aptitude is complex. Opinions on what one needs for musical aptitude and in what extent are varying (Shutter-Dyson & Gabriel 1981). Seashore (in 1938) emphasized a number of distinct and sharply defined talents (pitch, intensity, time, consonance, tonal memory, and rhythm) which can be present or absent in individuals in varying degrees. On the contrary, Wing (in 1968) believed in more general ability. Again, the tests of Gordon (in 1965) and Karma (in 1994) are both based on short phrases of music instead of unrelated sounds. Gordon gave as much value to the rhythmic, melodic and harmonic components of the music, and Karma defined musical aptitude as an ability to hear or perceive sound structures or sound patterns (Shutter-Dyson & Gabriel 1981).

Table 1. Seashore, Wing, Gordon and Karma tests for musical aptitude. Test name, subtests, number (N) of questions per test and reliability score. The tests used in our studies are in bold.

Test name	Subtests		N of questions	Reliability
Seashore measures of musical talents	**pitch**		**50**	**0.71**
	intensity		50	0.72
	time		**50**	**0.58**
	consonance		50	0.49
	tonal memory		30	0.83
	rhythm		30	0.54
Wing standardized tests of musical intelligence	chord analysis		20	
	pitch change		30	
	memory		30	
	rhythm		14	entire test 0.91
	harmony		14	
	intensity		14	
	phrasing		14	
Gordon musical aptitude profile	tonal imagery:	melody	40	
		harmony	40	
	rhythm imagery:	tempo	40	
		metre	40	entire test 0.92-0.95
	musical sensitivity:	phrasing	30	
		balance	30	
		style	30	
Karma music test				**0.88**

One reason to study musical aptitude is that it is a common and measurable phenotype in the general population. It is not as extreme as absolute pitch (AP) (an ability to recognize the pitch of a musical tone without a reference pitch), present in approximately 8-15 % of the population (Baharloo et al. 1998; Theusch et al. 2009), or amusia (tone deafness), present in approximately 4 % of the population (Peretz et al. 2007). Although studies on musical abilities have been carried out for over hundreds of years, scientific research on the biological basis of musical abilities is scarce.

2.1.5. Creativity in music

Creativity is a complex function of the human brain that varies in degree from an individual's small-scale creative insights to large-scale creative productivity with societal and economic aspects. Generally, creativity can be defined as an ability to produce work that is both original and appropriate for the situation in which it occurs (Guildford 1950; Sternberg 2006; Bengtsson et al. 2007; Hennessey & Amabile 2010). A characteristic of a creative individual is an ability to operate through the entire spectrum of personality dimensions, divergent thinking and discovery orientation. It has been proposed that creativity requires the presence of several traits, e.g. intelligence, perseverance, unconventionality, novelty seeking and the ability to think in a particular manner (Csikszentmihályi 1990; Csikszentmilhályi & Wolfe 2000; Bachner-Melman 2005). In some intelligence models creativity and divergent thinking are facets of intelligence (e.g. Jäger 1982 and Guilford 1967, 1979).

Music culture and industry depends on creativity in music. Composing, arranging, improvising and interpreting music by singing, playing an instrument or dancing are complex creative functions of the human brain, for which the biological value remains unknown. Bengtsson et al. (2007) reported that the pianist's cortical regions, such as the right dorsolateral prefrontal cortex, the pre-supplementary motor area, the rostral portion of the dorsal premotor cortex, and the left posterior part of the superior temporal gyrus, were activated while improvising. Further, prefrontal activity accompanied by widespread activation of neocortical sensory-motor areas was demonstrated in MRI studies of improvising professional jazz pianists (Limb & Braun 2008). More recently, in functional magnetic resonance imaging (fMRI) study of freestyle rap (lyrical improvisation) dissociated pattern of activity was seen within the prefrontal cortex and activation of left hemisphere language and motor control regions (Liu et al. 2012). Furthermore, in connectivity analyses amygdala showed its importance in improvisation (Liu et al. 2012).

Recently, vulnerability genes or risk alleles associated with psychiatric diseases have shown to act as plasticity genes, with the result that carriers are more affected by environmental influences (Belsky 2009). Especially, various dopamine (DA) and serotonin transporter (5-HTT) related genes have been associated with both psychiatric diseases and creativity (Carson 2011). Schizophrenia susceptibility genes catecol-O-methyltranferase (*COMT*), dopamin

receptor D2 (*DRD2*) and tyrosine hydroxylase 1 (*TPH1*) are reported to be associated with verbal, figural and numeric creativity (Reuter et al. 2006). In addition to this, neuregulin-1 polymorphism has been suggested to contribute to creativity (Kéri 2009). In the brain imaging study of de Manzano and colleagues (2010), the dopamine D2 receptor system and thalamic function proved to be important for creative performance (divergent thinking).

2.1.6. Studies on fetus and infants

The minimal effect of auditory experience in infants enables exploring of the innateness and universals of music in humans. Particular abilities or capabilities are suggested to be innate, as they appear in the early stages of development and in the absence of relevant experience. There is evidence that already at birth the neuronal architecture of an infant is ready to process music (Perani et al. 2010) and consonance is preferred over dissonance (Zentner & Kagan 1996; Perani et al. 2010). In the early months of life, music is preferred over speech and maternal singing over maternal speech (Trehub 2001). Further, many studies have shown that infants are capable of processing both pitch (Zentner & Kagan 1996; Trehub 2001; Perani et al. 2010; Homae et al. 2012) and temporal patterns (Trehub et al. 1995; Trehub 2001; Hannon & Trehub 2005; Zentner & Eerola 2010).

Brain processing of auditory information has been studied in infants, aged three to six months, using multichannel near-infrared spectroscopy (Homae et al. 2012). An infant's brain detects pitch changes in successive tones, that is, more than single tones of pitch information, showing sensitivity to pitch discrimination (Trehub 2001; Homae 2012). Further, the right temporoparietal region, involved in processing pitch changes in speech, was confirmed to be involved in processing of changes in auditory sequences. The study suggests increasing sensitivity of the infant's right temporoparietal region to auditory sequences with similar temporal structures to those of syllables in speech during development.

Rich metrical processing has been observed in infancy. Infants are flexible and discriminate speech sounds from languages they have never heard, but over the first year they become differentially responsive to a narrower range of speech. Studies on experience-dependent tuning in the domain of musical rhythm perception in infants at the age of six to seven months showed that rhythmic variations of foreign tunes posed no difficulty for infants (Hannon &

Trehub 2005). Infants of six months of age showed culture-general responding whereas infants from 11 to 12 months of age showed an adult-like, culture-specific pattern of responding to musical rhythms (Hannon & Trehub 2005). Hannon & Trehub (2005b) suggest that there is an appearance of sensitive period early in life, when learning is particularly rapid and behavior is modified easily facilitating infants aged 12 months to perceive rhythmic distinctions in foreign musical context more readily than adults.

Human infants are sensitive to rhythmic language patterns (Petitto et al. 2001) and this suggests that there is a basic neural architecture for rhythm perception that is independent of training (Limb et al. 2006). When rhythmic behavior (moving in synchrony to music, also referred to as entrainment) was studied with preverbal infants aged five to 24 months, they showed more rhythmic movement to music and other rhythmic sounds than with speech, suggesting a positive effect of rhythmic engagement with music (Zentner & Eerola 2010). These data support the suggestion that the capability of infants to interpret rhythm is innate. Rhythm in music evokes motor function in humans, but its biological basis remains poorly characterized (Chen et al. 2008). The capability to detect beat in rhythmic sound sequences seems to be functional already at birth (Winkler et al. 2009), it is detectable in three to four month olds and further evolves during the first year of life (Hannon & Trehub 2005; Winkler et al. 2009). Bouncing has been observed in infants not older than seven months (Phillips-Silver & Trainor 2005), suggesting an innate desire to move in time with music (Zentner & Eerola 2010). Physical movement in time with music requires vestibular system and auditory perception of the rhythm (Trainor et al. 2009), these in turn activate the motor and premotor corticles of the brain (Bengtsson et al. 2009). The ability to sense a regular pulse helps individuals to synchronize their movements with each other, this being necessary for dancing or producing music together, suggesting that rhythm perception and motor output boost social communication.

2.1.7. Music in the human brain

In neurobiological studies, music has been shown to be a powerful stimulus for the human brain (Blood & Zatorre 2001). Thus it provides a tool to study human cognition and its underlying brain mechanisms. For the brain music processing includes numerous cognitive tasks, including perception, social cognition, emotion, learning and memory (Koelsch & Siebel 2005; Menon & Levitin 2005; Zentner et al. 2008). Although, shared cognitive processes and neural substrates between music and language exist, pitch information processing differs between them (Zatorre & Baum 2012; Marcus 2012).

Although music has been shown to activate specific areas of the brain (Schneider et al. 2002; Tervaniemi et al. 2006), there is no clear "music center" in the brain (Figure 5). Brain areas responsible for music perception also serve other purposes, such as speech, emotions or reward (Marcus 2012). An exact understanding of how, when and where in the brain music is processed is still missing but different features of music, e.g. pitch and rhythm (time), have been shown to be processed by separate neural networks in many studies. In general, pitch processing is predominated by right hemisphere, whereas rhythm processing involves both hemispheres (Peretz et al. 2005; Zatorre et al. 2003; Hyde et al, 2009). Brain damage can harm the pitch discrimination skill while sparing the time discrimination and vice versa (Perez & Zatorre 2005). Furthermore, in congenital amusia there is deficiency in the processing of pitch, while time discrimination skill is normal (Foxton et al. 2006).

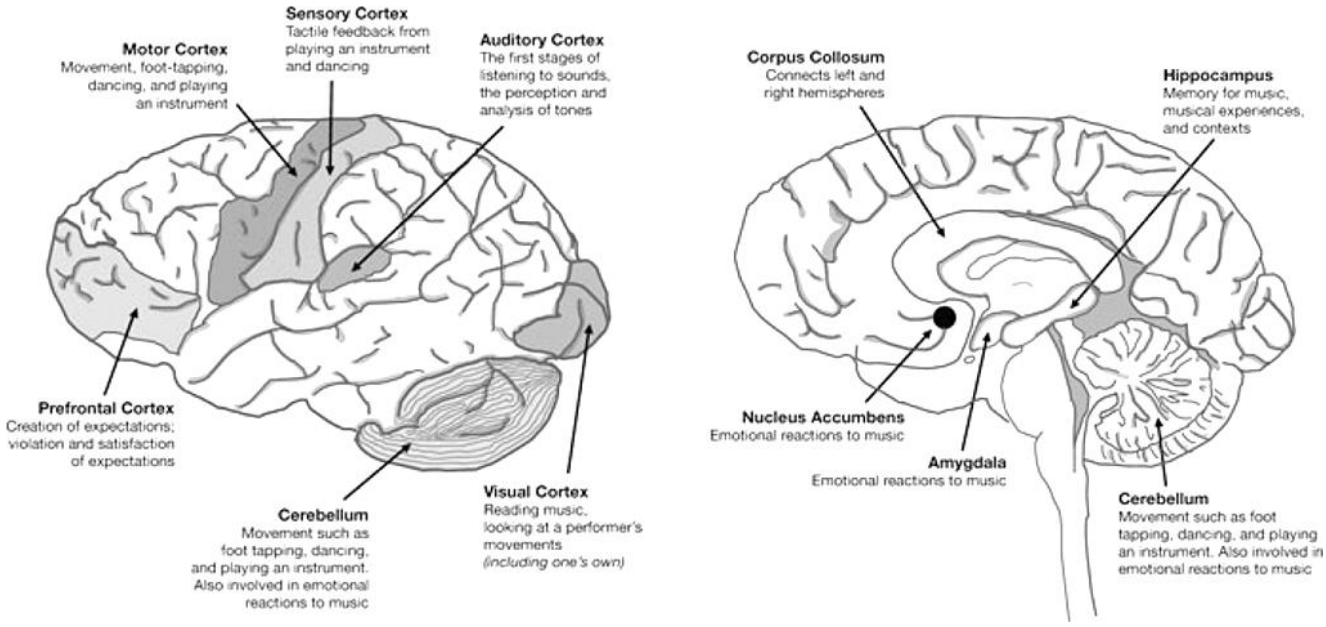


Figure 5. Core brain regions associated with musical activity. Reprinted with permission. Levitin & Tirovolas Annals of the New York Academy of Sciences 2009.

Brain imaging methods for studying the neural basis of music processing include electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Music has been studied by basically two approaches: which areas of brain are activated by music (see 2.1.7.1), and how do the brains of musicians and non-musicians differ (see 2.1.7.2).

2.1.7.1. Music as stimuli for the human brain

Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion (Blood & Zatorre 2001). Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions (Blood et al. 1999). In investigations using PET, music listening has been reported to cause physiological changes in cerebral blood flow, cardiovascular and muscle function (Blood & Zatorre 2001). Listening to music activates mesolimbic structures including the nucleus accumbens and the hypothalamus, the reward centers of the brain (Menon & Levitin 2005; Blum et al. 2010), but molecules mediating these effects remain so far uncharacterized. Novel, passively heard, pleasant musical stimuli elicit similar positive feelings and limbic activations (activation of subcallosal

cingulate gyrus, prefrontal anterior cingulate, retrosplenial cortex, hippocampus, anterior insula, and nucleus accumbens) as familiar favorites do in non-musicians (Brown et al 2004).

Pleasant music has been shown to promote release of dopamine (DA), endorphins and endocannabinoids (Boso et al. 2006). One physiological function experienced as a positive, even euphoric, emotion elicited by listening to music listening is musical chills. While experiencing the chills the activated brain areas relate to reward processes (areas in the dorsal midbrain, ventral striatum, insula, and orbitofrontal cortex etc.), similarly activated by other euphoria inducing substances like cocaine and chocolate (Zatorre 2003). However, the biological mechanism underlying these effects has not been elucidated.

The first study demonstrating DA release in man during normal human behavior was done in 1998 (Koepp et al. 1998). Evidence for endogenous DA release in the human striatum during a goal-directed motor task, in this case playing a videogame, was provided using PET. The videogame playing was associated with increases in regional cerebral blood flow values. Concerning music, the first study providing evidence that pleasure in response to listening to music is associated with dopamine release in the mesolimbic reward system of the brain (dorsal and ventral striatum) was the PET study of Salimpoor et al. (2011). The DA release resulted from the anticipation of the reward in response to music and the peak pleasure itself was pinpointed to distinct anatomical pathways (the caudate during the anticipation and the nucleus accumbens during the experience) using fMRI. Further, the peaks of autonomic neural system activity reflecting the most intense emotional moments and musical chills were shown to associate with DA release in the nucleus accumbens, the region responsible for the euphoric component of psychostimulants such as cocaine, and connected with limbic regions mediating emotional responses (Salimpoor et al. 2011).

2.1.7.2. Music alters brain function and structure

The lifelong ability to adapt to different environmental needs is based on the capacity of the central nervous system to plastic alterations. The structural and functional organization of an adult's brain is only to some extent determined by early development, and may be substantially modified through sensory experiences (Pantev et al. 2001). Since 1980s, not only numerous studies on humans, but also studies on animals have demonstrated

neuroplasticity at the molecular, synaptic and macroscopic structural levels (Jenkins et al. 1990; Recanzone et al. 1993; van Praag et al. 2000; Kilgard et al. 2001). The critical period for the development of musical skill has been discussed and in several studies music training at an early age has shown increase in grey and white matter volume in different brain areas (Munte et al. 2002). Musicians' brains provide valuable models in which to study neuroplasticity in the auditory and motor domains.

Listening to and/or playing music are environmental stimuli that have multiple measurable effects on brain structure and function. Studies comparing musicians and non-musicians have revealed structural and size differences in several brain regions, including the planum temporale, the anterior corpus callosum, the primary hand motor area and the cerebellum. Active training and practising music has been shown to enlarge cortical presentations in the somatosensory and auditory domains in professional musicians. The plastic changes were seen in the cortex specific for the fingers that were frequently used and stimulated in the playing of an instrument compared to controls (Elbert et al. 1995). Mismatch negativity (MMN) studies have suggested that musical training shapes the auditory cortex so that even minimal changes in auditory stimuli sequences are detected (Koelsch et al. 1999; Russeler et al. 2001; Tervaniemi et al. 2001).

Bengtsson et al. (2007) reported that pianist's cortical regions such as the right dorsolateral prefrontal cortex, the pre-supplementary motor area, the rostral portion of the dorsal premotor cortex, and the left posterior part of the superior temporal gyrus were activated while improvising. More recently, prefrontal activity accompanied by widespread activation of neocortical sensory-motor areas was demonstrated in MRI studies of improvising professional jazz pianists (Limb et al. 2008).

Music therapy has been used and studied for the past fifty years in the psychological and physiological health of individuals. In many studies, listening to or practicing music has shown to have a positive effect on cognitive tasks like episodic memory, working memory and creative problem solving tasks, possibly because of increased brain DA levels (McDermoot & Hauser 2005; Rickard et al. 2005; Särkämö & Soto 2012). Music therapy has been shown positive effect for anxiety, relaxation, stress, pain (Cole & LoBiondo-Wood 2012), and rehabilitation from stroke (Särkämö & Soto 2012). Further, it has shown to

improve communication skills in autistic children (Gold et al. 2006). Cole and LoBiondo-Wood (2012) suggested that music is safe, inexpensive and easy approach to pain control in hospitalized adults. However, the mechanism of music therapy is unknown.

2.1.8. Nature versus nurture

The genetic and environmental factors underlying musical aptitude and musicianship have been under debate for long time (Sloboda 1991; Gagné 1997; Marcus 2012). The well-known child prodigy phenomenon in the music field suggests that genetic differences do exist.

Musical aptitude is usually defined as the potential or capacity for musical achievement. Essential part of it is individuals' capacity to discriminate changes in pitch, time and timbre. Evidently, the capacity varies between individuals (Karma 2002), which is a typical feature of a complex trait influenced by several underlying genes with varying effects, possible environmental factors and their interactions. Studies have shown evidence of familial aggregation of the traits, like absolute pitch (Baharloo et al. 1998; Theusch et al. 2009), musical pitch recognition (Drayna et al. 2001) tone deafness (Peretz et al. 2007), and musical aptitude (Pulli et al. 2008). Many studies have shown that young infants respond strongly to music and even newborn infants are capable of perceiving musical sounds (Hannon & Trehub 2005; Trehub 2006). This suggests that the ability to perceive music is an innate trait and is transmitted in the genes. The opposite point of view is the suggestion that only intense practice, extended for a minimum of ten years or 10,000 hours would make a talent (Ericsson 1993). Definitely, practice alone cannot explain the existence of exceptional child prodigies, like Mozart, whose exposure to music is far less. Evidently, not all of us become proficient musicians even through explicit training (Ericsson 1993). Recently, there has been growing interest in genetic linkage and association studies in families and twins, which could also enable discerning between genetic and environmental effects as well as possible gene-environment interactions (Engelman et al. 2009). The central question of this debate has shifted to a more sophisticated question: To what degree are various types of musical ability influenced by genetic and environmental variation?

In contrast to simple monogenic traits, which follow Mendelian laws, complex traits have a polygenic and environmental aetiology. The same phenotype can be a result of an unknown

number of genes, environment, and their complex interactions (Laland et al. 2010; Rowe & Tenesa 2012). Polygenic traits can be measured quantitatively and they typically vary along a continuous gradient. Musical aptitude is most probably one of them. This hypothesis is supported by the fact that in the general population musical aptitude is normally distributed; both extremes (highly capable and incapable) are rare and the majority expresses moderate ability (Karma 2002). Another complex cognitive trait, intelligence, is similarly distributed in the population like musical aptitude and has been shown to be influenced by both genes and the environment (Plomin & Loehlin 1989; Plomin & Thompson 1993; Deary et al. 2009; Davies et al. 2011; Deary et al. 2012; Loo et al. 2012).

Gene-environment interactions (G x E) occur when the effect of a person's genes depends on the environment and/or the effect of the environment depends on a person's genotype (Dick 2011; Duncan et al. 2011). The effects of shared genes and shared environment have been discriminated using family, twin and adoption studies (Almasy & Blangero 2010). Twin studies have shown that different cognitive abilities such as learning, reading and mathematics have strong genetic influence (0.41-0.60) (Haworth, et al. 2009). Twin and family studies have successfully been used to determine the heritability (h^2) of traits. Heritability is defined as the proportion of the total variance of the phenotype that is genetic ($h^2=V_G/V_P$, where V_G is genetic variance and V_P is overall variance of the phenotype). In the first study of musical pitch recognition, h^2 was estimated to be from 0.71 to 0.81 (Drayna et al. 2001), using the Distorted Tunes Test (DTT), where short popular melodies are played correctly or incorrectly and judged by listener. No dominant genetic effect or effect of shared environment was detected (Drayna et al. 2001). Later, in multigenerational Finnish pedigrees the heritability of musical aptitude was estimated to be 0.48 for combined music test scores, 0.42 for KMT, 0.57 for Seashore pitch discrimination (SP), and 0.21 for Seashore time discrimination (ST) (Pulli et al. 2008), see also chapter 2.1.4 in this thesis.

Absolute pitch (AP) is defined as an ability to recognize the pitch of a musical tone without a reference pitch. Both early musical training in early childhood and genetic predisposition are needed for the development of AP (Gregersen et al. 1999; Gregersen et al. 2001). In the family-based study of Profita and Bidder (1988), AP was suggested to be inherited as an autosomal dominant manner with incomplete penetrance. Baharloo et al. (1998) reported that nearly all study members with AP started musical training by the age of six. The families

supported the same inheritance pattern as in Profita and Bidder (1988). The sibling recurrence risk (λs) for AP is ~8-15 % (Baharloo et al. 2000).

Another extreme phenotype, congenital amusia (tone deafness) is a deficit in detecting pitch changes in melodies. It affects 4 % of the population. Perez et al. (2007) showed a hereditary component in amusic families, that is 39 % of first-degree relatives have the trait whereas only 3 % have it in control families (λs=10.8; 95 % confidence interval 8-13.5). Thus the recurrence risks of amusia and AP are actually very similar to each other, "symmetric", if one may say so, for the opposite ends of the ability spectrum.

While the biological research on music has traditionally been based on neurophysiological methods, lately musical traits have been associated with several loci and variants (Pulli et al. 2008; Theusch et al. 2009; Park et al. 2012) in genome.

2.2. Structure of the human genome

The genome sequence of any two individuals is identical to 99 %. The remaining 1 % varies from single nucleotide polymorphisms (SNPs) to larger chromosome anomalies or even aneuploidy of an entire chromosome (Venter et al. 2001; Redon et al. 2006). Small scale point mutations can be classified as substitutions, insertions or deletions of single base pairs, whereas larger chromosomal alterations are typically duplications, deletions, inversions or translocations. Genetic variation in individuals arises through mutations, random combination of male and female gametes during fertilization, and independent assortment of chromosomes with crossovers during meiosis. Mutations create novel alleles, whereas other mechanisms create unique combinations of alleles (Table 2).

Linkage disequilibrium (LD) arises from the evolutionary history of the population and it is a sensitive indicator of the population genetic forces that structure a genome. LD means non-random combination of alleles at different loci on a chromosome. Thus, LD mapping can be used to map genes that are associated with quantitative characters and inherited diseases, and to understand past evolutionary and demographic events (Slatkin 2008).

Table 2. Types of genomic variation.

Variation type	Definition	Frequency in the human genome
Single nucleotide polymorphism (SNP) (Studies I, II and IV)	Single base pair variation found in >1 % of chromosomes in a given population	over 18 million SNPs in the human population (dbSNP 137)
Insertion/deletion variation (InDel)	Deletion or insertion of a segment of DNA. Includes small polymorphic changes and large chromosomal aberrations. InDels >1 kilobases(kb) in size are often also called CNVs	about 1 million insertion/deletion polymorphisms >1 basepairs (bp) in the human genome
Microsatellite (Studies I and II)	Sequences containing variable numbers of 1-6 bp repeats totaling <200 bp in length	>1 million microsatellites in the human genome, accounting for about 3 % of the sequence
Minisatellite and variable numbers of tandem repeats (VNTRs) (Studies I and II)	Polymorphic sequence containing 20-50 copies of 6-100 bp repeats	about 150,000 minisatellites, of which about 20 % are polymorphic
Intermediate-sized structural variant (ISV)	Gain or loss of a DNA sequence >8 kb in size also includes inversion breakpoints	297 ISVs were identified using a fosmid library from a single genome
copy number variation (CNV) (Study III)	Copy number change >1 kb.	12 % of the human genome (360 megabases) is covered by CNV regions (Redon et al. 2006)
Inversion	Rearrangement causing a segment of DNA to be present in reverse orientation	Estimates of microscopically detectable inversion frequencies are 0.12-0.7 % (pericentric) and 0.1-0.5 % (paracentric); sub-microscopic unknown
Translocation	Rearrangement in which a DNA fragment is attached to a different chromosome	1/500 is heterozygous for a reciprocal translocation and 1/1000 for Robertsonian translocations
Unbalanced rearrangements	Rearrangements which lead to a net gain or loss of DNA are referred to as unbalanced	Unbalanced rearrangements occur in about 1/1500 live births

2.2.1. Genetic mapping

Genetic mapping is concerned with identifying genetic loci that contribute to diseases or traits of interest. Basically there are two approaches for genetic mapping: linkage and association methods. In linkage, genetic markers are used to show how a chromosomal segment is inherited through a pedigree (Strachan & Read 2010). The aim is to identify co-segregation between genetic markers and the studied trait. Association is, basically, correlation between marker alleles and a trait in a population. Of these approaches, neither generally leads to a direct identification of a gene underlying the phenotype but only indicate its most likely position in the genome.

2.2.1.1. GWS or candidate gene studies

There are two categories of strategies commonly used to search for genes underlying complex traits, which are caused by interplay of predisposing genes and environmental factors (Risch & Merikangas 1996; Plomin et al. 2009): candidate gene studies and genome-wide studies (GWS). With the latter, whole genome is sequenced, or genotyped using a vast number of polymorphisms. A candidate gene approach can be utilized when there is, for example, biochemical evidence for a protein or enzyme to be involved with the trait. The candidate gene can be screened with a set of markers or by re-sequencing the gene. Candidate genes may also be identified from chromosomal regions that are first pinpointed by other means, such as genome wide linkage analyses or chromosomal aberrations. Association, linkage or re-sequencing approaches can be used for both candidate gene studies and GWS.

Genome-wide association studies (GWAS) consist of several hundreds of thousands or millions of SNPs that are spread over the whole genome. Every locus is tested against the trait resulting in hundreds of thousands of tests in GWS. Along with the increasing number of statistical tests performed the number of false positive associations also increases. Thus, GWAS come with multiple testing problem and the traditional p-value thresholds of 0.01 or 0.05 are thus far too liberal. With Bonferroni correction or permutation the significant threshold for genome-wide has been suggested to be $p < 5 \times 10^{-7}$ (Risch & Merikangas 1996; Freimer & Sabatti 2004).

Using GWAS and candidate gene analyses numerous human traits and diseases have been shown to be influenced by several genetic loci (Wellcome Trust Case Control Consortium 2010). However, the effect sizes of the alleles identified throughout GWAS are commonly small. GWAS of complex phenotypes rely on the "common disease –common variant" (CD-CV) hypothesis, but more recently the focus is being shifted to the "rare variants –common disease" (RV-CD) hypothesis (Marian 2012). CD-CV supposes that complex phenotypes result from cumulative effects of a large number of common variants with a modest effect. In contrast, RV-CD surmises that multiple rare variants with large effect sizes are the main determinants. The development of methods in quantitative genetics and gene mapping has facilitated the identification of genes affecting complex human traits. Lately, GWAS have identified >250 genetic loci where common genetic variants occur that are reproducibly associated with polygenic traits or diseases (Hirschhorn 2005; McCarroll & Altshuler 2007; Wellcome Trust Case Control Consortium 2007; Ott et al. 2011).

Most of GWAS have focused on disease genes and less interest has been shown in normal variation in human. The cognitive abilities of individuals differ and many such differences among individuals are shown to be highly familial (Davies et al. 2011). Gene mapping approaches with complex cognitive traits has been performed for example in intelligence. The fMRI twin study by Koten and colleagues (2009) suggested genetic contribution to differences in cognitive function. Further, a longitudinal MRI twin study by Brans et al. (2010) reported that variation in human brain size is highly heritable. Thinning of the frontal cortex and thickening of the medial temporal cortex with increasing age was shown to be heritable and partly related to cognitive ability. Genes influencing variability in intelligence and brain plasticity were partly driving these associations (Brans et al. 2010).

The first GWAS of intelligence was performed by Davies et al. (2011). The analysis of ~500 000 SNPs showed that variation in human intelligence is significantly influenced by common SNPs being in linkage disequilibrium (LD) with causal variants. The longer chromosomes showed, on average, larger effect on the trait. Analysis of individual SNPs and genes yielded one genome-wide significant association ($p = 9.2x10^{-7}$) with formin-binding protein 1-like (*FNBP1L*). It is strongly expressed in neurons, including hippocampal neurons, in developing brain and it regulates neuronal morphology. The study shows for the first time that human

intelligence is a biological trait that is highly polygenic with many genes having an additive effect (Davies et al. 2011).

In this thesis, both candidate gene and GWS approaches were used, with (family based) association methodology. Additionally, heritabilities of the traits were studied via variance-component methods created for quantitative trait linkage (QTL) mapping in pedigrees.

2.2.1.2. Association and linkage

The aim of linkage analysis is to explore co-segregation of the trait of interest and marker alleles (Terwilliger & Ott 1994). Co-segregation can be studied in e.g. sib-pairs or families. Recombination events between markers flanking the disease gene narrow down the chromosomal region. Two-point linkage analysis is performed between individual markers and a trait, whereas multipoint analysis concerns several adjacent markers and the trait, and may be more informative than the former approach. Linkage analyses can further be classified as either parametric or non-parametric. In parametric linkage analysis (also called model-based) knowledge about the mode of inheritance, recombination fraction, penetrance of the causal allele, causal allele frequency, and marker allele frequencies have to be specified prior to analysis. In Mendelian monogenic diseases these analyses have been successful but with complex phenotypes or diseases true values of these parameters are most often unknown, and misspecification of the model may hamper the analysis. In contrast, non-parametric analyses (also called model free) are more suitable for studying complex phenotypes because specification of inheritance model, penetrance or risk allele frequencies are not needed (Ott et al. 2011). Variance component methods are non-parametric, model free, and are suitable for extended pedigrees. The idea of variance component method is that phenotypically similar relatives are likely to share more alleles compared to expected sharing probabilities at affective locus. With this method, polygenic, environmental and monogenic effects for trait variability can be estimated. Parametric methods may have more power than non-parametric but there is risk of choosing genetic model wrong. Linkage analysis programs for quantitative traits used in this thesis include Merlin (Abecasis et al. 2002) and SOLAR (Almasy & Blangero 1998).

In association analysis the statistical correlation between genetic markers and the trait are examined. Significant overrepresentation or underrepresentation of an allele in affected vs.

unaffected subjects is taken as evidence for genetic association. Association analysis can be divided into two approaches; direct association and indirect association. Direct association means that the genotyped polymorphism itself is the cause for the trait, which may be the case in a candidate gene study. Indirect association concerns genotyping of markers in LD with the causal allele. Transmission disequilibrium test (TDT) is widely used method for qualitative trait analysis in trios and larger pedigrees (Spielman et al, 1993). Program packages for family-based association studies include e.g. family-based association test (FBAT) based on TDT (Lange et al. 2004; Laird & Lange 2006) and quantitative transmission disequilibrium test (QTDT) based on regression (Abecasis et al. 2000). GenAbel (Aulchenko et al. 2007) and UNPHASED (Dudbridge 2008) program packages which are based on TDT and can handle missing data.

There is a long-standing controversy of method superiority between linkage and association methods. Association analysis can be either based on case-control samples of unrelated individuals, or family based samples (Laird & Lange 2006) or both. Association analysis is considered to be an effective method (Ott et al. 2011) in studies where common variant causes (Risch & Merikangas 1996) common phenotype. Association studies have also been suggested to be more suitable for common complex traits caused by several susceptibility genes with modest impact size (Risch & Merikangas 1996; Hirschhorn & Daly 2005; Ott et al. 2011). Compared to population data, the use of family data in association analysis may even give higher power (Laird & Lange 2006). It must though be noted that the advantages of a family-based setting over case-control or population data include possibilities to observe genotyping errors in the form of Mendelian inconsistence, control of population stratification, enrichment of rare variants and the ability to discriminate variants co-segregating with the trait (Antoniou & Easton 2003; Ott et al. 2011). Although large families contain lots of information, they can be computationally problematic.

Combination of methods provided by linkage and association studies bring up the most robust and powerful approach to identify variants for traits (Ott et al. 2011). Still, the results of GWS and linkage results are always probabilistic. To confirm results additional proof is needed in the form of replicate studies, candidate gene studies and functional studies.

2.2.2. Copy Number Variation

Copy number variations (CNVs) are structural genomic variants arising from deletions or duplications of genomic regions. Thus, CNVs are observed as copy-number changes of the respective genomic region from the usual state of two copies per genome to zero, one, three, or more than three copies. CNVs range from a few kilobases (kb) to megabases (Mb) in size (Redon et al. 2006). Non allelic homologus recombination (NAHR) mediated by the presence of repeated sequences is one mechanism of CNV formation (Stankiewicz & Lupski 2010). The improved resolution of the methods for detecting CNVs has led to the observation of even smaller sized CNVs, nowadays typically less than 50 kb long. CNVs have been suggested to have multiple effects on gene function, evolution and disease risk (Feuk 2006; Redon et al. 2006). Dosage-sensitive genes residing in CNV areas may cause altered gene expression possibly rendering susceptibility to a disease. Diseases caused by CNVs of dosage-sensitive genes critical for functions of the nervous system have been identified (Almal & Padh 2012).

To date, CNVs have been shown to have an important role in neuropsychiatric disorders (Sebat et al. 2007; Itsara et al 2009; Salyakina et al. 2011; Magri et al. 2010; Karlsson et al. 2012; Marshall et al. 2012) and in common complex disorders (Blauw HM et al. 2010; Conrad et al. 2010; Wellcome Trust Case Control Consortium 2010; Shia WC et al. 2011; Park JH et al. 2012). The majority of CNV studies has been performed in case-control settings and has focused on diseases (Wellcome Trust Case Control Consortium 2010; Salyakina et al. 2011; Karlsson et al. 2012), whereas family-based studies on normal cognitive traits are rare. Recently, CNVs underlying normal human traits, like height and intelligence, have been studied (Dauber et al. 2011; Yeo et al. 2011).

Experimental techniques detecting CNVs from genome include bacterial artificial chromosome (BAC) arrays, paired end mapping, fluorescent in situ hybridization, representational oligonucleotide microarray analysis (ROMA) and whole genome single nucleotide polymorphism (SNP) arrays (Iafrate et al. 2004). Today, SNP arrays are the most common tool for studying CNVs. Several methods have been developed to detect CNVs from genome-wide SNP array data. The multi-algorithm approach for detecting CNVs increases the confidence of CNV calls and reduces false positives (Dellinger et al. 2010; Pinto et al. 2010; Pinto et al. 2011).

2.3. Molecular genetics of musical traits

2.3.1. Previous genome-wide scans of musical aptitude

The first genome-wide linkage study of musical aptitude was performed in 15 Finnish families with a total of 234 family members using 1113 microsatellite markers (Pulli et al. 2008). The study suggested a major locus for musical aptitude: significant evidence of linkage was found at chromosome 4q22 (maximum LOD score 3.33) and suggestive at chromosome 8q13-21 (maximum LOD score 2.29). Several other regions with suggestive linkage were also found (Figure 6). This was the first study showing genomic regions in linkage with musical aptitude.

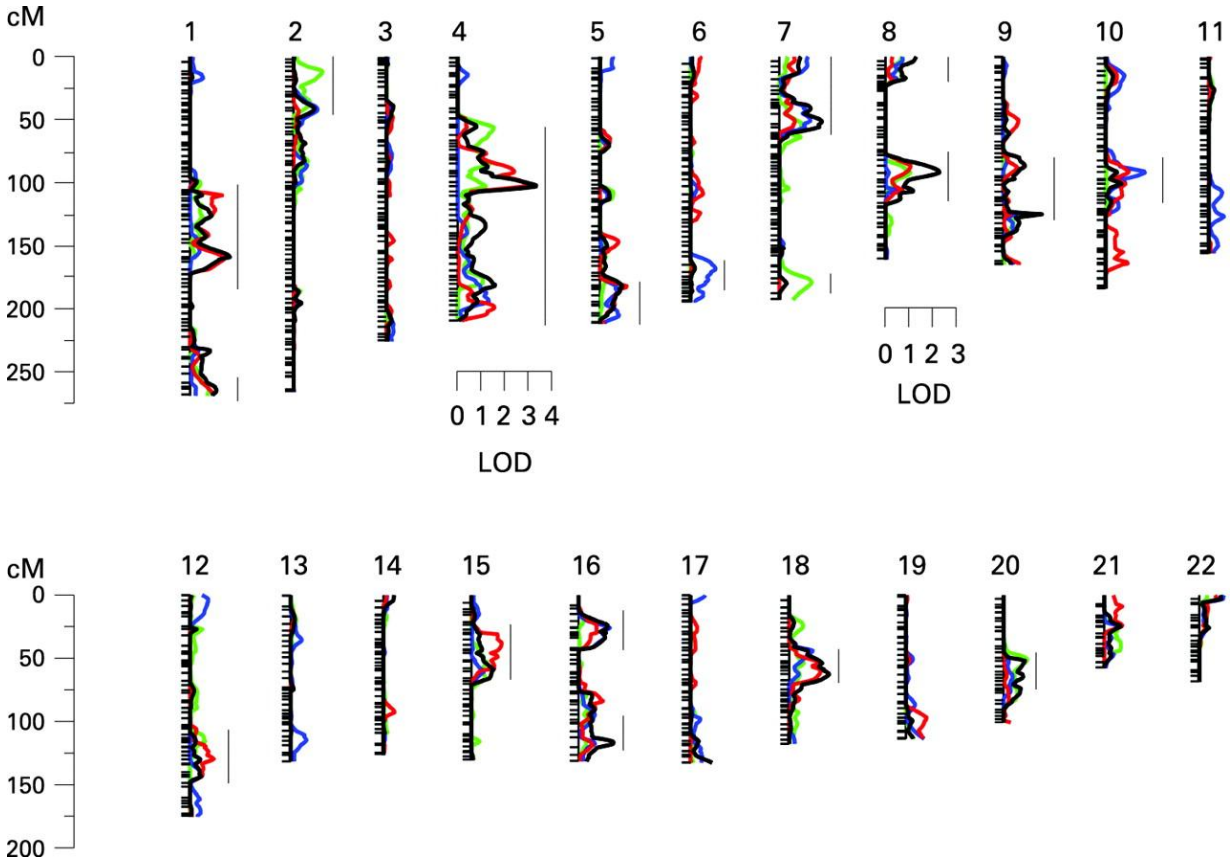


Figure 6. LOD scores from the genome-wide linkage study of musical aptitude by Pulli et al. (2008). The marker map is based on the decode genetic map. Chromosomal locations with LOD scores >1 with any of the traits (KMT (red), SP (blue), ST (green) and/or COMB (black) are shown by a vertical line. Reprinted with permission Pulli et al. J Med Genet 2008.

The second genome-wide study of musical ability was performed by Park et al. (2012). Here, the data consisted of 73 extended families with a total of 1008 individuals from Mongolia, as part of the GENDISCAN project, which was designed to discover genetic influences on complex traits in a population isolate from North East Asia. The musical ability phenotype was defined based on the pitch production accuracy test (PPA), where a pitch produced by a device is recited by an individual after hearing it through a headset. Family-based genome-wide linkage analyze was performed with 862 samples from 70 families genotyped with the deCODE (Iceland) 1039 microsatellite marker panel. The heritability of musical ability explained by the additive genetic portion was estimated as 40 %. The maximum LOD score 3.1 was found from chromosome 4q23 with the nearest marker D4S2986. The putative linkage region ranged from 99 cM to 118 cM. In the next phase, family based association analysis was carried out in 630 family members from 53 extended families, using an Illumina SNP array containing 620,000 markers per sample. Age and sex were used as covariates in all analyses. The strongest association was found for rs12510781 ($p=8.4x10^{-17}$), located near the gene UDP glycosyltransferase 8 (*UGT8*), playing a part in the synthesis of the myelin membrane of the central and peripheral nervous systems. Further, significant association between musical ability and SNPs near genes ELOVL fatty acid elongase 6 (*ELOVL6*) and alpha-kinase 1 (*ALPK1*) was found (Figure 7). In order to search for functionally significant variants in the candidate genes, the authors used exome sequence data of 40 founders and 180K array-based comparative genomic hybridization results from 30 founders, both of which were included in the study and previously genotyped. Among the 347 SNPs and seven indels discovered by exome data in the putative linkage region, four SNPs were in strong LD with the SNPs with highest associated SNPs. In particular, the non-synonymous SNP rs4148254 was found to have the most significant association with musical aptitude ($p=8.0x10^{-17}$). At the level of CNVs a 6.2 kb deletion near *UGT8* showed a plausible association with musical ability ($p=2.9x10^{-6}$).

Intriguingly, the genome-wide analyses performed separately in Finnish and Mongolian populations with different music phenotypes (musical aptitude and musical ability) revealed linkage in the partly overlapping genetic regions at chromosome 4q (Figure 7) (Pulli et al. 2008; Park et al. 2012).

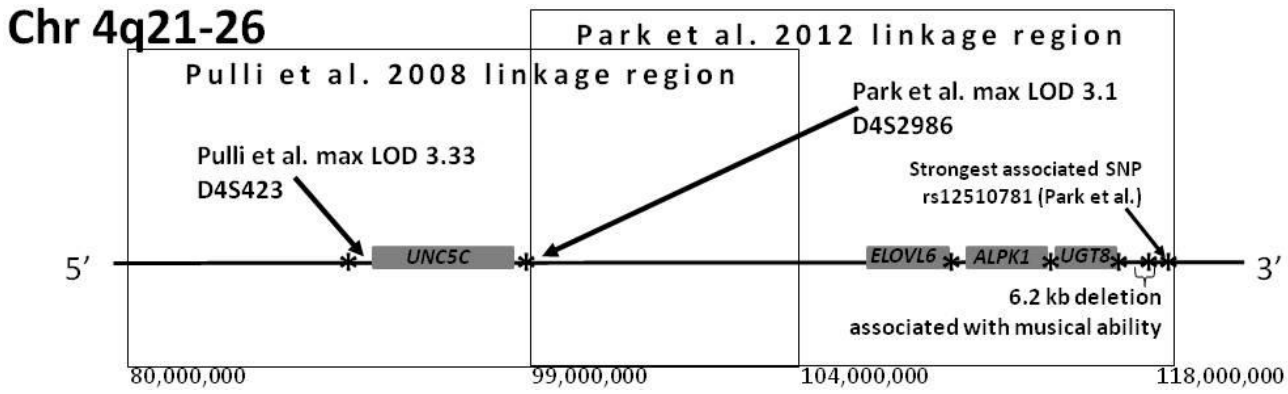


Figure 7. The linkage regions of genome-wide studies of musical aptitude and musical ability at chromosome 4q. The regions observed in two studies are partly overlapping. The maximum LOD score regions of both studies are located near gene *UNC5C*. Association analysis of Park et al. (2012) linkage region obtained significant results for genes *ELOVL6*, *ALPK1* and *UGT8*. Asterisks (*) denote SNPs associated with musical ability in Park et al. (2012).

2.3.2. Genome-wide scan of absolute pitch

The genome-wide study of absolute pitch, by Theusch et al (2009), was performed on 73 multiplex AP families with 281 individuals genotyped with 6090 SNP markers. With the subset of 45 families with European ancestry, non-parametric multipoint linkage analysis revealed loci in 8q24.21 (LOD score 3.46, empirical genome-wide p=0.03). Other regions with suggestive LOD scores included chromosomes 7q22.3, 8q21.11 and 9p21.3. Obviously, these traits (AP, musical aptitude etc.) are genetically heterogeneous.

The results of previous genome-wide studies of music related traits are summarized in the Table 3.

Table 3. Major results from published genome-wide studies of various music traits.

Phenotype	Chr	LOD	Ref.
Musical aptitude			Pulli et al. 2008
Combined music test scores	4q22	3.33	
	8q13-21	2.29	
	18q	1.69	
Karma music test	4q22	2.91	
Seashore time	4q22	1.18	
Seashore pitch	10	1.67	
Musical ability (pitch production accuracy test)	4q23	3.10	Park et al. 2012
Absolute Pitch	8q24.21	3.46	Theusch et al. 2009
	8q21.11	2.24	
	7q22.3	2.07	
	9p21.3	2.05	

2.3.3. Previous candidate gene studies for musical traits

2.3.3.1. AVPR1A and SLC6A4

The selection of genes for examination in candidate gene association studies for music related traits has been based on prior assumptions about underlying biology. So far, only two candidate gene studies for music related traits have been published (Granot et al. 2007; Morley et al. 2012). Both of them have explored polymorphisms of the arginine vasopressin receptor 1A (*AVPR1A*) and the serotonin transporter 6A4 (*SLC6A4)* genes.

The *AVPR1A* gene encodes for a receptor for a neuropeptide, which mediates the influence of the evolutionally well preserved hormone arginine vasopressin (AVP) (Van Kesteren et al. 1995) in the brain (Wassink et al. 2004). AVP has an important role in memory and learning (Fink et al. 2007). *AVPR1A* has been shown to modulate social cognition and behavior (Donaldson & Young 2008; Veenema & Neumann 2008), including attachment, social bonding and altruism in humans and other species (Donaldson & Young 2008). *AVPR1A* gene contains the highly variable microsatellite markers RS3 (corresponding to $(CT)_4$-TT-$(CT)_8(GT)_{24}$) and RS1 (corresponding to $(GATA)_{14}$) residing in the promoter region and AVR (corresponding to $(GT)_{14}(GA)_{13}(A)_8$) microsatellite in the intron of the gene (Figure 8).

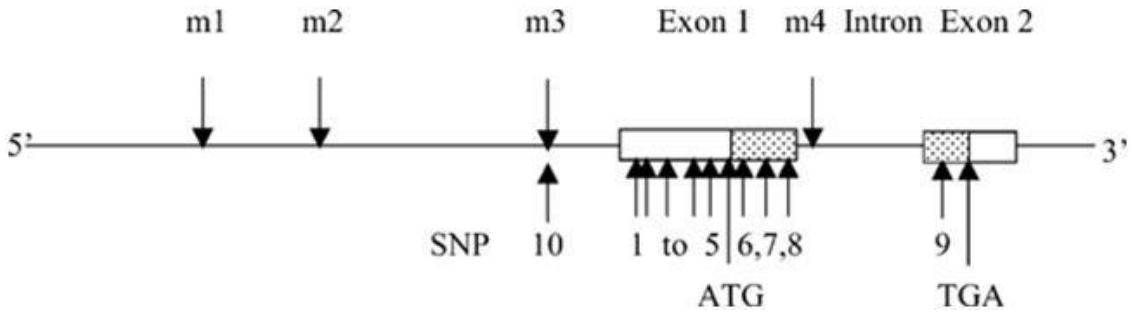


Figure 8. Schematic drawing of *AVPR1A* gene with microsatellite markers: m1= $(GT)_{25}$, m2= RS3, m3= RS1 and m4= AVR. RS3 and RS1 are residing in the promoter region and AVR in intron of the gene. SNPs 1 to 10, start codon ATG and stop codon TGA represented. Reprinted with permission Kim et al. Molecular psychiatry 2002.

The importance of dopaminergic and serotonergic system, and related genes, for cognitive and motor functions have been shown in human (Reuter et al. 2006; Bachner-Melman et al. 2005; Barnett et al. 2007) and animal studies (Rauceo et al. 2008). The human serotonin transporter is expressed mainly in the brain areas involved with emotions in cortex and limbic systems. The role of the serotonin-transporter-linked polymorphic region (5-HTTLPR), located in the solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 gene (*SLC6A4*), has previously been studied in reward-seeking behaviors (Kremer et al., 2005), and in emotional disorders (Hu et al. 2006; Zalsman et al. 2006). Polymorphisms of *SLC6A4* together with *AVPR1A* have been associated with artistic creativity in professional dancers (Bachner-Melman 2005) and with short-term musical memory (Granot et al., 2007).

The first candidate gene study explored promoter region polymorphisms of *AVPR1A* and *SLC6A4* genes and musical memory (Granot et al. 2007). Participants were 82 university students (21 males and 61 females) with little or no musical training. The music tests lasted for 2.5 hours and they included testing of e.g. melodic and rhythmic memory, phonological skill, the melodic imagery subtest from Gordon's Musical Aptitude Test (see chapter 2.1.4), the tonal memory test from Seashore, an adapted version of the DTT (see chapter 2.1.8), and the rhythmic tests from the Seashore and Gordon battery of tests. The study was the first one to suggest that promoter region repeats of *AVPR1A* and *SLC6A4* are associated with short-term memory for music.

Later on, Morley et al. (2012) studied *AVPR1A* and *SLC6A4* in the case-control study of choral singers and non-musicians. Out of 523 participants, 262 reported practicing choral singing in an amateur choir and 261 were non-musicians (hospital staff, patients, doctors etc). A variable number tandem repeats (VNTR) polymorphism in the *SLC6A4* gene showed overall association with singer/non-musician status (p=0.009); the 9-repeat (p=0.04) and the 12-repeat (p=0.04) alleles were more common in singers, while the 10-repeat (p=0.009) was less common among singers. Because no association was found between other studied polymorphisms and the trait, the authors suggested that choir membership may depend partly on factors other than musical aptitude (Morley et al. 2012).

2.3.4. Molecular genetic studies on creativity

Data about molecular genetic studies on creative functions is scarce. The only molecular genetic study on creative functions which can be related to music was performed in professional dancers. Creativity in professional dancers was studied with *AVPR1A* and *SLC6A4* polymorphisms (2.3.3.1) (Bachner-Melman et al. 2005).

Currently, there are two other studies exploring the genetic variants in creativity. The high heritability of intelligence and the relationship between intelligence and creativity (correlation up to 0.50, Cropley 1966) led to the first candidate gene study for creativity (Reuter et al. 2006). Dopamine and serotonin related genes tryptophan hydroxylase 1 (*TPH1)*, catechol-O-methyltransferase (*COMT)* and dopamine receptor D2 (*DRD2)* were chosen as candidates (Reuter et al. 2005). The study sample consisted of 92 healthy Caucasian subjects. Creativity was assessed by the "inventioneness" test of the Berlin Intelligence structure test measuring the components of figural, verbal and numeric creativity and challenges, flexible production of ideas, the power of imagination and problem solving skills. *TPH1* is responsible for production of peripheral serotonin. The *TPH1* A779C polymorphism has also been associated with an addiction (Reuter et al. 2005). The role of dopamine receptor D2 gene (*DRD2*) has been studied in several cognitive processes, including intelligence (Weinshilboum & Raymond 1977; Grandy et al. 1993; Reuter et al. 2006; Shaw 2007), learning from errors (Klein et al. 2007), and creativity in humans (Reuter et al. 2006). The *DRD2* TaqI restriction-fragment-length polymorphism (TaqIA) has two categories, homozygous variant (A1) and

presence of wild-type allele (A2) (Wong et al. 2000). The carriers of the A1 allele (A+) have shown D2 dopamine receptor density reduced up to 30–40% compared to A1- (Weinshilboum & Raymond 1977). In the study of creativity, allele A1+ of *DRD2* was related to higher verbal creativity as compared to the A1- allele ($p = 0.032$), and the carriers of the A allele of *TPH1* A779C polymorphism showed significantly higher scores in figural ($p = 0.019$) and in numeric creativity ($p = 0.036$) than those with the other allele. Furthermore, polymorphisms of *DRD2*, and *TPH1* genes were associated with total creativity (*DRD2* TaqIA $p = 0.071$, A1-allele $p = 0.027$; *TPH1* $p = 0.044$, A-allele $p = 0.012$). Herein, *COMT* was not associated with any of the creativity scores in this study.

The other study concerning molecular genetics of creativity was performed by Kéri (2009). Here, a polymorphism of neuregulin 1 (*NRG1*), a candidate gene for psychosis, was associated with creativity in people with high intellectual and academic performance. The highest scores from creative achievements and creative-thinking questionnaires were found from participants with the psychosis risk genotype T/T (SNP rs6994992) (Kéri 2009).

In this study, we examined whether these genes that are closely related to cognitive brain function are associated with musical aptitude and/or creative functions in music.

3. AIMS OF THE STUDY

The overall aim of the present study was to explore the molecular genetic background of musical aptitude in Finnish families.

The following specific aims were addressed in this study:

I. To use both genetic and questionnaire data from study subjects and estimate the heritability and relationship of musical aptitude, creativity in music and listening to music in Finnish families (I, II)

II. To investigate the role of five candidate genes, *AVPR1A*, *SLC6A4*, *COMT*, *DRD2* and *TPH1* in musical aptitude, creativity in music and listening to music (I, II)

III. To identify copy number variations (CNVs) in musical aptitude and creativity in music using a genome-wide approach in both family-based and case-control settings (III)

IV. To perform a genome-wide scan to identify genetic variants for creative functions in music (IV)

4. MATERIALS AND METHODS

4.1. Family materials

The families for this study were recruited via nationwide searches. The first recruitment was completed during the years 2003-2009 by sending information leaflets or letters to families whose members had studied or were studying at the Sibelius Academy or other musical institutes in Finland. Thus, there were at least some professional musicians or active amateurs in each recruited family. The first recruitments led to the inclusion of families 1 to 19. Further recruitments were done in 2010 and 2011, this time with open invitations in newspapers, as we were interested in population variation and in obtaining both musical and unmusical individuals as well as subjects with and without music education. The second recruitments led to the inclusion of families 20 to 92. Families no.1-19 participated in study I, families no.1-31 in study II, families no.1-92 in study IV, and five of the biggest families and an additional 172 unrelated individuals in study III. Families no.1-15 have been depicted in Pulli et al. (2008, web only appendix), families no.16-19 in the study I and families no.20-31 in study II. Examples of the pedigrees collected in different recruitments are described in Appendix I.

The characteristics of the study material are described in Table 4. The data consists of a total of 92 extended families with 412 family members. Each family includes from 2 to 50 family members from 1 to 4 generations. Participants over the age of 7 years were tested for musical aptitude and DNA was collected from participants over the age of 12 years.

Table 4. Main characteristics of the study samples.

Used in publication	I	II	III	IV
N of families	19	31	5 and unrelated	92
N of study subjects	343	437	170 and 172	412
N of DNA samples	298	416	170 and 172	412
Sex distribution*	44 % (M); 56 % (F)	45 % (M); 55 % (F)	48 % (M); 52 % (F); **41% (M);** 59 % (F)	41 % (M); 59 % (F)
Age range; mean	9-93 years; 43 years	8-93 years; 42 years	≥12 years	12-94 years

* M=male; F=female; ** unrelated

4.2. Phenotyping

4.2.1. Musical aptitude

Musical aptitude of the participants were determined by three music tests: the auditory structuring ability test (KMT) (Karma 2007) and Carl Seashore's pitch and time discrimination subtests (SP and ST respectively) (Seashore et al. 1960) as described in detail in Pulli et al. (2008) and in the studies I-III. The music tests used in this study were chosen by music experts of our research group so that they measure as many different aspects of musical aptitude as possible. The test session lasted for an hour during which music tests were played through loudspeakers.

KMT contains 40 items and is designed to measure recognition of melodic contour, grouping, relational pitch processing and gestalt principles, the same potentially innate musical cognitive operations reported by Justus and Hutsler (2005). Each rhythm and melody containing item, played by various instruments, is played three times and after that a reference sequence is played once (Figure 9). Each participant listens to the recorded test items and marks on the paper if the reference is the same or different from the item played first. Three sample items of KMT can be listened from the internet at the homepage of the research group (http://www.hi.helsinki.fi/music/naytteet.htm). The Seashore's tests each contain 50 items that measure sensory capacities, such as the ability to detect small differences in tone pitch (Seashore pitch, SP) or duration (Seashore time, ST) that are necessary in music perception. In each of the Seashore's tests the test tone is first played once and after that comes a reference tone. KMT scores were multiplied by 1.25 to allow direct comparison with

Seashore's tests. All tests we used measure music perception skills, not production (Seashore et al. 1960; Shutter-Dyson & Gabriel 1981; Karma 1994; Karma 2004).
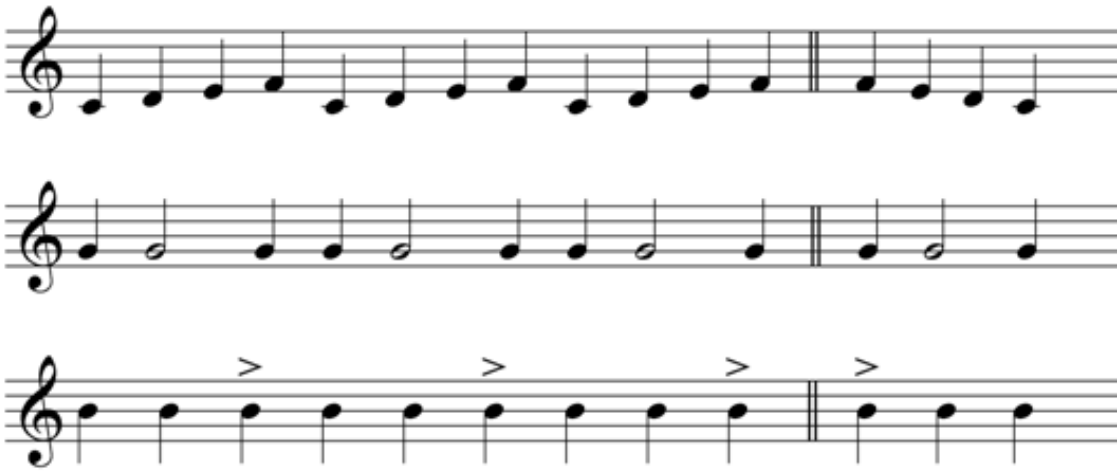


Figure 9. Three examples of Karma music test items (one line each). Each item is played three times, and then comes the comparison phrase. After this the question if the first played is same or different is answered.

In order to summarize the variation of three tests into one statistical measure, a combined music test score (COMB) was computed as the sum of the separate scores of the three individual test results (range from 75 to 150 scores). In the study of Pulli et al. (2008) the reliabilities for the music test scores were: KMT 0.88, SP 0.91 and ST 0.78. The youngest participants of the age of nine years or less had the lowest music test scores (on average KMT 23.0, SP 35.6 and ST 33.4) while the group of 9-11 years old were scored on the same level as those aged over 12 years (Pulli et al. 2008)

The music tests used here are not able to separate real talents form well-scoring individuals (Shuter-Dyson & Gabriel 1981). The individuals with high musical aptitude tend to gain equally high scores. Thus, this study does not consider talents. For this purpose other music tests should be used.

4.2.2. Environmental factors

Obviously, environmental factors play an important part in an individuals' musical ability. Music education that one had at preschool, lessons for instrument playing at young age, the parents' attitude towards music and the music one heard as a child may play a role in an individuals' musical aptitude. In this study these factors were assessed by a questionnaire in which the background information of the participants was collected (Table 5). An invitation letter to the questionnaire was sent by e-mail (if available) or by traditional mail. The letter contained information about the research, the URL (Uniform Resource Locator) to the web site at University of Helsinki where the questionnaire was accessible and instructions on how to open the web site and answer the questionnaire. A printed questionnaire was also available. Parents answered the questions on behalf of their children who were younger than 12 years of age.

One part of the questionnaire evaluated the music education of the participant. Participants were asked if he/she ever attended music lessons, preschool music lessons, private lessons for music instrument, studied in some music university or sang in a choir, etc. To dissect listening habits, active and passive listening of music were separately defined and surveyed. Active listening was defined as attentive listening of music, including attending concerts. Passive listening was defined as hearing or listening to music on background. Additionally, more detailed information (e.g. musical training in general) was asked to confirm other answers in each participant. Further, practicing of creative functions in music, i.e. composing, improvising and/or arranging music was asked. We did not find it necessary to define the degree of one's creativity but simply to ascertain if a participant considers that he/she practices creative functions in music.

Table 5. The background questionnaire of the study.

1. MUSICAL EDUCATION (Please, choose appropriate alternatives, mention age and instrument)
A) I have never played any instrument or sung in a choir
B) Some private instrumental or singing lessons:
C) Music preschool/kindergarten:
D) Music class/music oriented school:
E) Music school:
F) Conservatory or polytechnic:
G) Music university (e.g. Sibelius Academy):
H) I have sung in a choir/played in an ensemble or band:
I) institute of adult education:
J) No music lessons but I am a self-taught music amateur
K) Any other education in music, what?
2. HOW MANY HOURS DO YOU LISTEN TO MUSIC WEEKLY (AN AVERAGE)? Please, fill the table to the appropriate extent. It is important to know any possible changes in your listening habits during the life. Active listening = attentive listening of music, including attending concerts. Passive listening = hearing or listening to music as background music.
A) ACTIVE LISTENING (hours per week)
childhood about
at age 12—20 about
at age 21—30 about
at age 31—40 about
at age 41—59 about
at age 60— about
B) PASSIVE LISTENING
childhood about
at age 12—20 about
at age 21—30 about
at age 31—40 about
at age 41—59 about
at age 60— about
C) What is your favourite music? (Music genre or favourite band/artist)
3. HOW MANY HOURS DO YOU PLAY/SING/PRACTISE MUSIC A DAY? (hours per day)
A) Currently
B) Earlier (e.g. during student days)
4. OTHER MUSIC ACTIVITIES (choose the appropriate alternatives)
A) I compose music
B) I arrange music
C) I improvise music
D) Something else, what?
5. WHY DO YOU LISTEN TO MUSIC OR GO TO CONCERTS? (Choose the appropriate alternatives)
A) I listen to music in order to relax or to feel good
B) I choose different kinds of music for different emotional states

C) I listen to music in order to study new pieces of music
D) I listen to music to concentrate better while working or studying
E) I have other reasons for listening to music, what?
6. DO YOU ENJOY PERFORMING i.e. SINGING OR DANCING FOR OTHER PEOPLE?
A) No, I avoid situations where I have to perform
B) No, but I have to perform now and then
C) Yes, I enjoy performing for other people
D) Yes, performing motivates me
E) Other reasons to avoid performing/to perform, what?
7. HOW OFTEN DO YOU PERFORM i.e., PLAYING, SINGING OR DANCING TO OTHER PEOPLE?
A) Never
B) Once a year
C) Once a month
D) 2—3 times a month
E) Once a week
F) More often
G) I am a professional musician and performing music is my job
8. DO YOU DANCE, DO MUSIC GYMNASTICS OR SOME OTHER EXERCISES IN TIME WITH MUSIC?
A) Never
B) Once a year
C) Once a month
D) 2—3 times a month
E) Once a week
F) More often
G) I am a professional dancer/dance teacher
9. DO YOU THINK YOU ARE MUSICAL (e.g. compared with your siblings, friends, and parents)?
A) No
B) Yes and I think the strongest feature of my musicality is:

4.2.3. Laboratory methods

Peripheral blood samples for genomic DNA extraction were drawn from participants over 12 years of age. The study was approved on18th April 2008 by the Ethical Committee of Helsinki University Central Hospital (permission #469/E7/2002). An informed consent was obtained from all participants. Each participant was coded with a unique ID-number; no names were used during the analyses. Genomic DNA was extracted from peripheral blood with standard phenol-chloroform procedure (Maniatis et al. 1982). Primer sequences were designed using the Primer3Plus (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi/) program (Rozen et al. 2000).

Candidate gene analysis

The DNA of the study subjects was amplified by polymerase chain reaction (PCR) under standard conditions and in annealing temperatures specific for primers (Table 6) in studies I and II. After PCR *DRD2* TaqI polymorphism amplicons were digested using 5 U of TaqI restriction enzyme NcilI FastDigest (Fermentas, Vilnius, Lithuania) incubating 37 min in 5 °C and inactivating 80°C for 20 min (Grandy et al. 1993). The 310 bp, 180 bp and 130 bp long digestion products were resolved by electrophoresis in 5.0 % MetaPhor agarose (Cambrex Bio Science Rockland). SNP sequencing of *COMT* and *TPH1* polymorphisms were performed using cycle sequencing with the Exo Sap-It (Affymetrix, Santa Clara, CA, USA) and Big Dye Terminator v.3.1 (Applied Biosystems, Foster City, CA, USA) –enzymes.

Microsatellites (see Table 2) were used as molecular markers in studies I and II. The highly variable microsatellites RS3 and RS1 residing in the promoter region and the AVR microsatellite in the intron of the *AVPR1A* gene and microsatellites VNTR in the promoter region and 5-HTTLPR in the intron 2 of the *SLC6A4* gene were analyzed using the GeneScan-500 LIZ (Applied Biosystems, Foster City, CA, USA) size standard. Both sequencing and microsatellite reactions were run on an ABI 3100xl (Applied Biosystems, Foster City, CA, USA) capillary sequencer. SNPs were analyzed with Sequencer 5.0 (Gene Codes Corporation) software and microsatellites with GeneMapper 4.0 software (Applied Biosystems, Foster City, CA, USA).

Table 6. Primers and conditions used for genotyping in studies I and II.

Gene	Marker	Region	Forward primer	Reverse primer	Tm (°C)
AVPR1A	RS3	12q14-15, promoter	5'-FAM-CCT GTA GAG ATG TAA GTG CT-3'	5'-TCT GGA AGA GAC TTA GAT GG-3'	60
AVPR1A	RS1	12q14-15, promoter	5'-VIC-AGG GAC TGG TTC TAC AAT CTG C-3'	5'-ACC TCT CAA GTT ATG TTG GTG G-3'	60
AVPR1A	AVR	12q14-15, intron	5'-FAM-ATC CCA TGT CCG TCT GGA C-3'	5'-AGT GTT CCT CCA AGG TGC G-39	60
SLC6A4	VNTR	17q11.2, promoter	5'-FAM-TCAGTATCACAGGCTGCGAG-3'	5'-TGTTCCTAGTCTTACGCCAGTG-3'	66
SLC6A4	5-HTTLPR	17q11.2, intron 2	5'-GGCGTTGCCGCTCTGAATGC-3'	5'-GAGGGACTGAGCTGGACAACC-3'	58
DRD2	TaqIA RFLP	11q23.1	5'-CCGTCGACGGCTGGCCAAGTTGTCTA-3'	5'-CCGTCGACCCTTCCTGAGTGTCATCA-3'	53
COMT	val158met	22q11.2	5'-GGGCCTACTGTGGCTACTCA-3'	5'-GGCCCTTTTTCCAGGTCTG-3'	60
THP1	A779C	11p15.3-14	5'-CCATTACTAAAGTATTATCACCC GATCAT-3'	5'-CAAGCCAATTTCTTGGGAGAAT-3'	61

Genome-wide analysis using SNPs

Genome-wide analysis of CNVs and SNPs in musical aptitude and creativity in music were performed using Illumina Human OmniExpress 12 1.0V SNP chip (Illumina Inc., San Diego, CA, USA). Using this platform over 700,000 SNPs were genotyped per each subject. Illumina GenomeStudioV2010.3 (Illumina Inc., San Diego, CA, USA) was used to generate the final report. Genotyping failed in 2 samples and they were removed from the analysis.

4.2.4. Statistical analyses

4.2.4.1. Quality control of genotyping

Genotype incompatibilities were searched with PedCheck 1.2.1.23 (O'Connel & Weeks 1998). Hardy–Weinberg equilibrium (HWE) was tested with PEDSTATS (Wigginton & Abecasis 2005). Marker allele frequencies were estimated by maximum likelihood in multigenerational families with SOLAR (Almasy & Blangero 1998). IBD allele sharing probabilities were computed in a multipoint fashion using Simwalk2 (Sobel & Lange 1996) software package. Quality control of study IV was performed with GenAbel (Aulcenko et al. 2007).

4.2.4.2. Family-based association tests (FBAT/HBAT, UNPHASED)

In studies I and II, FBAT/HBAT (http://www.hsph.harvard.edu/fbat/fbat.htm) version 2.0.2c was used to calculate family-based association statistics for music test scores, creativity in music, listening to music and haplotypes. FBAT/HBAT (family-/haplotype-based association test) is a freely available program package allowing to use a wide range of data from different genetic relationships (nuclear families, sib ships, pedigrees etc., even incompletely genotyped) and phenotypes (dichotomous, quantitative or censored). It offers bi- and multi-allelic tests of association using standard genetic models (additive, dominant, recessive or genotype). in the first stage, a statistic to test for association between the trait locus and the marker locus is specified. In the second stage, the distribution of the genotyped marker data is computed by treating the offspring genotype data as random, and conditioning on parts of the data (Horvath et al. 2001). FBAT tests for association and linkage in a pedigree, using the general Z statistic (Laird et al. 2000), which is based on a linear combination of offspring genotypes and traits. The null hypothesis is "no association and no linkage" between the marker locus and any trait-influencing locus. The alternative hypothesis states there is both association and linkage. FBAT handles pedigrees by breaking each into nuclear families, and evaluating their contribution to the test statistic independently. All the results of studies I and II were controlled for multiple testing using permutation on FBAT/HBAT.

Further, a Linkage Disequilibrium Analyses for Quantitative and Discrete Traits software (QTDT) was used in study I to ensure the results for quantitative phenotypes evaluated with FBAT/HBAT (http://www.sph.umich.edu/csg/abecasis/QTDT/). QTDT incorporates variance components methodology in the analysis of family data and includes exact estimation of p-values for analysis of small samples and non-normal data. Linkage and association are considered simultaneously and QTDT also enables taking covariates into consideration when evaluating the genetic association (Abecasis et al. 2000).

HBAT cannot handle more than 80 different haplotypes at a time, thus multiallelic haplotypes (*AVPR1A* and *SLC6A4*) were analyzed using the program UNPHASED version 3.1.4 (Dudbridge 2008). UNPHASED was used in study II. UNPHASED is a suite of programs for association analysis of multilocus haplotypes from unphased genotype data. It was used to analyze associations at the haplotype level with pedigree disequilibrium test. The power of UNPHASED to detect strong effects is said to be high as it can handle missing data. Genotypes at frequencies lower than 0.05 were excluded (Dudbridge 2008). In addition to the default, that is, the additive model of gene function, dominant and recessive models were also tested.

In addition, sex and age were routinely used as covariates in all analyses. Additional covariates used for association analyses with e.g. creativity phenotype, were COMB scores and/or music education.

4.2.4.3. CNV detection and analyses

All the probe coordinates in study III were mapped to human genome build GRCh37/hg19. CNVs were identified using two Hidden Markov Model (HMM) -based algorithms, PennCNV and QuantiSNP, which currently constitute the most reliable set-up for CNV detection using Illumina SNP array platforms (Dellinger et al. 2010). Additionally, the multi-algorithm approach increases the confidence of CNV calls and reduces false positives (Dellinger et al. 2010; Pinto et al. 2010; Pinto et al. 2011). Quality control for the data was stringent at both sample-level and CNV-call level. Only larger than 10 bp long CNVs identified by both PennCNV and QuantiSNP were merged into a single consistent-call using

the outermost boundaries defined by either of the algorithm, irrespective of their size of overlap and retained only for further analyses.

The impact of CNVs on musical aptitude and creative functions in music was analyzed using three different approaches. 1) The transmission of CNVs in extended pedigrees and their penetrance in opposite extreme phenotypes (i.e. high COMB vs. low COMB and creative vs. non-creative subjects). Copy number variable regions (CNVRs) larger than 10 kb were ranked in each family for the "affected" individuals. This ranking method was described earlier by Karlsson et al. (2012). 2) The effect of CNV burden (number and size) on 172 unrelated individuals. 3) Association analysis between CNVs and the music phenotypes in unrelated individuals. All statistical analyses were performed using R (http://www.r-project.org/), SPSS software, PLINK and custom scripts.

4.2.4.4. Genome-wide association analysis

In study IV, GWAS of creative functions in music was performed with GenAbel (version 1.7-2) that is an R program for association analysis (Aulcenko et al. 2007). GenAbel is a fast association method that uses a mixed models method to correct for a family structure. The GRAMMAR algorithm (Svisheva et al. 2012) was used.

5. RESULTS AND DISCUSSION

5.1.Descriptive statistics and heritability of music traits (I, II, III, IV)

The basic statistics of the study participants are given in Table 4. Musical aptitude was measured using three music tests (KMT, SP and ST) (see 4.2.1). KMT consists of short phrases of "music" or rhythms while SP and ST are pair-wise comparisons of physical properties of sounds that measure somewhat simpler sensory capacities. The COMB music test scores varied from 75 to 150 scores (Figure 10). The mean of the scores was 122. Music education had an effect on music test scores; the distribution of the music test scores in the groups of less educated individuals were more close to normal distribution. In this study, the overall distribution of the music test scores is not normal because the most of the individuals who attended the study practiced music or at least were interested in it.

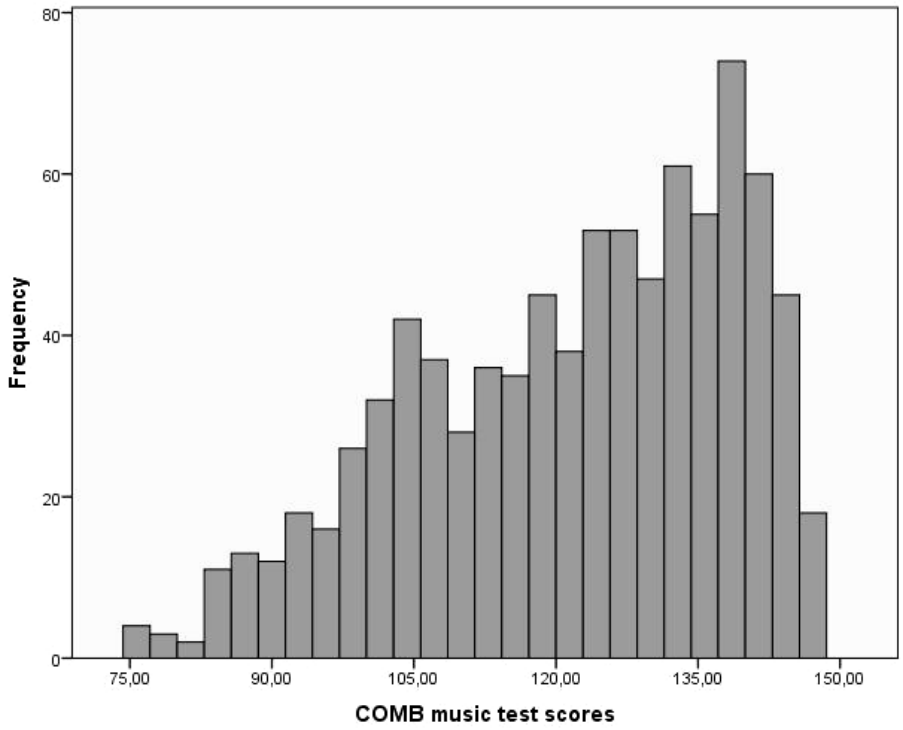


Figure 10. The combined music test scores (COMB) and their frequencies in 915 individuals.

The correlations between music test scores ranged from 0.41 between SP and ST, 0.48 between KMT and ST to 0.62 between KMT and SP (the p-value for correlations of all three < 0.001) (Figure 11). Correlations between the three tests show that the tests are measuring somewhat different parts of musical aptitude. Thus, calculating a combined music scores (COMB) from them was justified.

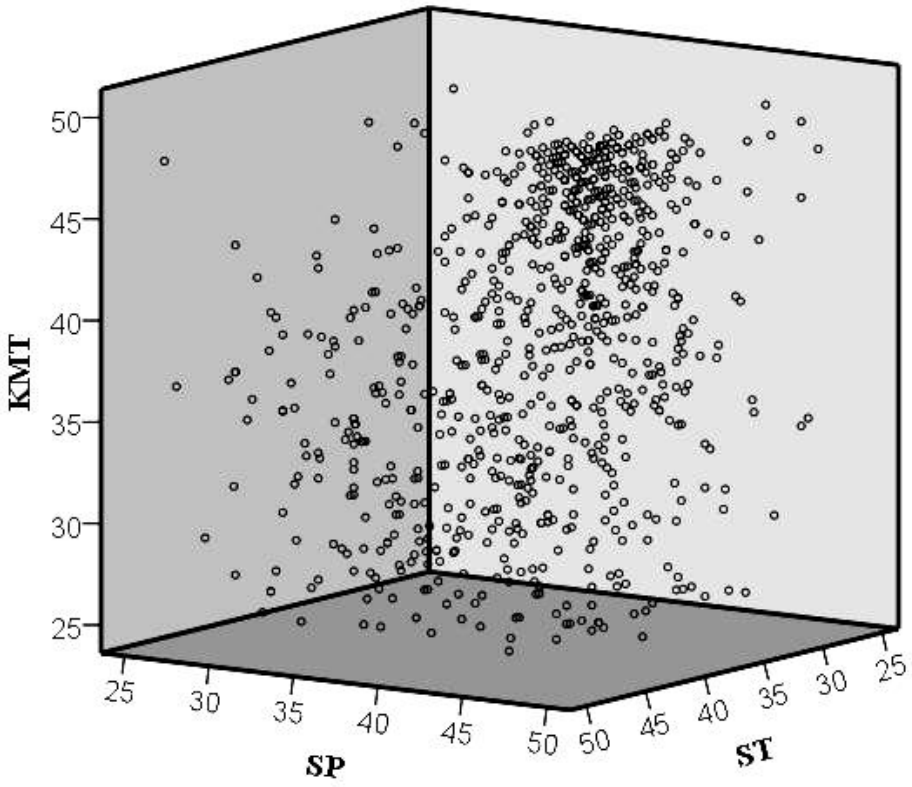


Figure 11. The joint distribution of the three music tests in 915 individuals. KMT= Karma music test, ST= Seashore time and SP= Seashore pitch. Combined music test scores were calculated as the sum of all three.

The age of the study subjects was found to affect the music tests scores (see Figure 12). The youngest and the oldest subjects yielded somewhat lower scores than the rest, which is in accordance with the results from many other studies concerning cognitive tests (Karma 2007; Tervaniemi et al. 2007; Dearly et al. 2012). Previously, Pulli et al. (2008) reported that already, subjects at the age of 9 years scored on the same level as older subjects. This and

other studies (Tervaniemi et al. 1997; Karma 2007) suggested that the maturation of the brain for musical aptitude occurs relatively early. In these studies, however, the oldest cohorts were not included so we cannot compare our results concerning the older age with them. In our study, the low test scores of the oldest generation may be due to hearing problems and the fast tempo of the test patterns whereas the lower scores of the youngest probably can accumulate from their shorter span of concentration and in some cases from difficulties in understanding the tests.

Additionally to age, sex was found to be correlated with one of the music tests; females had on average slightly lower scores in ST than males (mean ST males 41.9 points vs. females 39.6 points, correlation 0.191, $p < 0.001$). Based on these considerations, sex and age were used as covariates in association studies.

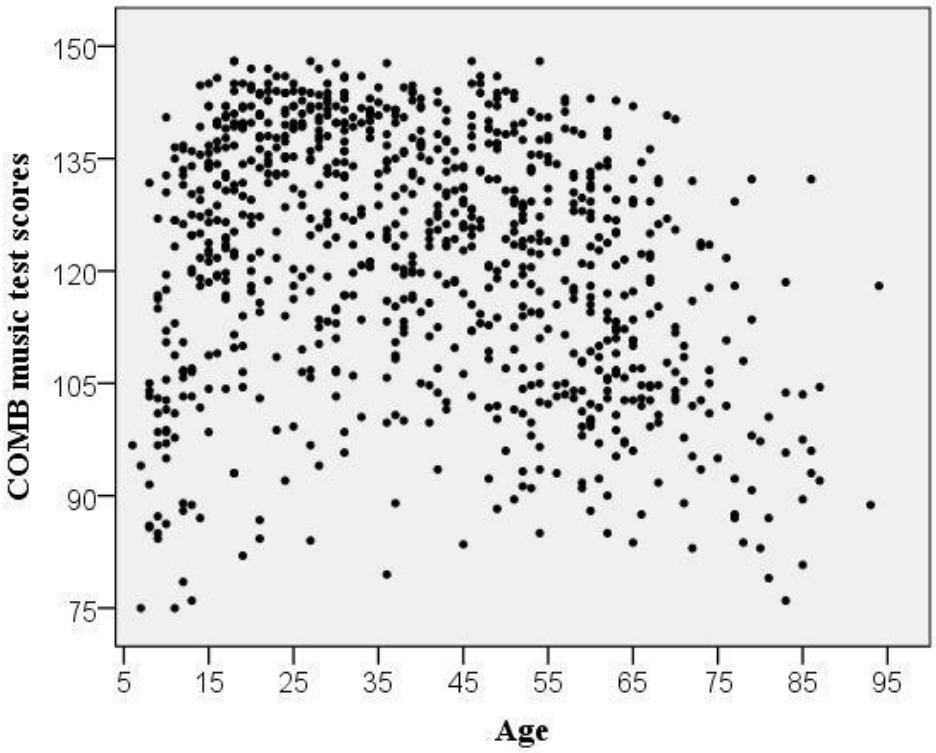


Figure 12. Music test scores are affected by age (N=864). The youngest and the oldest generation had the lowest music test scores.

In study I, creative functions in music (composing, improvising or arranging music) were associated with high scores in music tests (Figure 13) (Mann-Whitney KMT $p < 0.001$, SP $p < 0.001$, ST $p < 0.001$ and COMB $p < 0.001$). In our dataset, creativity in music was seen mainly in individuals with high music test scores, while the music test scores of non-creative individuals ranged through the whole scale. Based on this observation, creative functions in music are only present when there is also musical aptitude, though musical aptitude alone is not sufficient for creativity in music. This obviously raises an interesting question: what turns a high aptitude individual musically creative?

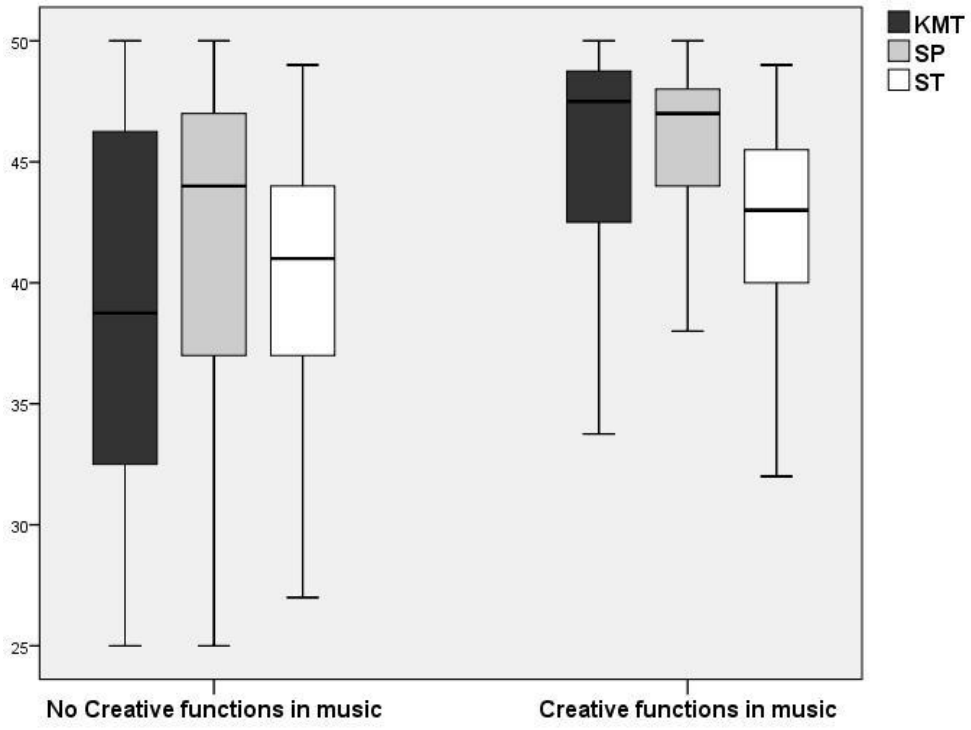


Figure 13. Music test scores are related with creative functions in music. Non-creative N=361 and creative N=149 in music. Y-axis: music test scores (dark bar KMT= Karma music test, gray bar SP= Seashore pitch and light bar ST= Seashore time). Bars showing the mean and error bars of each music test score.

In study I, creative functions in music were common in some of the pedigrees (e.g. no. 7, 9, 13 and 14) and absent from others (e.g. no. 2, 3, 5 and 8). Thus, creative functions in music showed substantial genetic component (overall creative functions in music heritability h^2 = 0.84; composing h^2 = 0.40; arranging h^2 = 0.46; improvising h^2 = 0.62). A strong genetic component was also seen in musical aptitude (COMB h^2 = 0.44; KMT h^2 = 0.39; SP h^2 = 0.52; ST h^2 = 0.10).

Study II was designed to explore patterns of listening to music, which had been surveyed in the questionnaire (Table 5). Quite evidently, an overall increase in music listening (hours per week) from the early decades of the 1900's to present times was observed. Thus, listening to music hours were standardized inside each age cohort. Secondly, within each decade the teenagers (at the age of 12-20 years) were the most eager music listeners. To minimize the effects of inaccuracy in remembering the amounts of listening, an overall average lifetime active and passive listening per individual was calculated as a simple mean of the standardized weekly amount of listening in different time categories. On average the participants lifelong active listening to music was 4.6 hours per week and passive 7.3 hours per week. Interestingly, amounts of mean listening varied between pedigrees. Intriguingly, pedigrees no. 13 and no. 14 showed enrichment of individuals with both creative functions in music and high amounts of active listening to music. Not surprisingly, an individuals' high amount of active listening to music correlated with the high level of music education.

Obviously, there were some possible sources of error which should be taken into consideration. First of all, we do not claim that music tests used here are the only tests which can be used for measuring musical aptitude. The three music tests used in this study only partially cover the phenotype. An ideal test would measure pure innate ability but such test may not exist. The background information was collected using web-based background questionnaire, which allows to collect data quickly and in a format that is easy to analyze, but at the same time there may be non-serious responses, additional drop-outs etc´. In our study, a paper version of the questionnaire was also available and the answering percent was high.

5.2. Candidate genes for musical aptitude, creative functions in music and listening to music (I, II)

In study I, association of eight polymorphisms of five candidate genes (*AVPR1A, SLC6A4, COMT, TPH1* and *DRD2*) with musical aptitude and creative functions in music was explored in 19 Finnish families with 298 genotyped members. An overall haplotype association was discovered with *AVPR1A* gene (markers RS1 and RS3) and KMT (cp = 0.00002), SP (p = 0.0072) and combined music test scores (COMB) (p = 0.0006) (Table 7). Further, *AVPR1A* haplotype AVR RS1 suggested a positive association with ST (p = 0.00184) and COMB (p = 0.0040). Arranging music was suggestively associated with *AVPR1A* haplotype AVR RS1 (p = 0.0039), composing with *TPH1* (p = 0.0107) and improvising with *COMT* (p = 0.0120). All p-values were corrected for multiple testing using permutation.

Study II continued to explore the association of candidate genes *AVPR1A* and *SLC6A4* with listening to music in larger study material. Finnish families (N=31) with 437 members (Table 4) were analyzed using family-based association method (FBAT). Sex and age were used as covariates in all analyses. Additional covariates, used for specific association analyses, were combined music test scores of the three music tests KMT, SP and ST, and/or music education. *AVPR1A* haplotype (RS1 and AVR) was associated with active current listening to music (p= 0.0019). Other *AVPR1A* haplotype (RS3 and AVR) showed association with lifelong active listening to music (p= 0.0022). *SLC6A4* showed no association with listening to music. All p-values were corrected for multiple testing using permutation.

The associations of the *AVPR1A* gene with the studied music phenotypes are combined in Table 7.

Table 7. Allele and haplotype associations of the *AVPR1A* gene microsatellite markers RS3, RS1 and AVR with music phenotypes. p-values are corrected for multiple testing using permutation. Only values p <0.01 are shown, the most prominent ones in bold. Note: "over all" indicates that not only a haplotype but the combination of the two markers is associated. Otherwise, the associated haplotypes of each microsatellite are given. KMT= Karma music test, SP= Seashore pitch, ST= Seashore time and COMB= combined music test scores.

Trait	RS3	RS1	AVR	Frequency/ informative families	p
KMT		ove	rall		0.02751
		4	4	0.103/20	0.02751
	ove	rall			0.00612
	4	4		0.042/11	0.01920
	5	**4**		**0.103/21**	**0.00002**
	4	**5**		**0.063/10**	**0.00032**
SP	5	4		0.103/21	0.00720
	4	5		0.063/10	0.01540
ST		**4**	**5**	**0.149/28**	**0.00184**
	4		4	0.052/11	0.00534
COMB		ove	rall		0.04546
		4	5	0.149/28	0.00402
	ove	rall			0.64910
	5	**4**		**0.103/21**	**0.00060**
	4	**5**		**0.063/10**	**0.00064**
Creativity in music, arranging		3	4	16	0.00379
current active listening	2			0.050/15	0.00995
	2		5	0.028/11	0.00434
		5	**5**	**0.096/19**	**0.00190**
	2	3		0.020/10	0.00256
	o ve	r a l l			0.00904
current passive listening	3	3		0.043/11	0.00886
	5		4	0.019/3	0.00816
lifelong active listening		5		0.110/30	0.00692
		5	5	0.096/19	0.00730
	6	4		0.017/6	0.00221

The same allele of *TPH1* gene here tentatively associated with composing was previously reported to associate with figural and numeric creativity (Reuter et al. 2006). Various genes related to dopamine and serotonin transporters have been previously associated with both psychiatric diseases and creativity (Reuter et al. 2006; de Manzano 2010; Carson 2011).

Previously, *AVPR1A* has shown to modulate cognition and behavior (Donaldson & Young 2008). *AVPR1A* is responsible for mediating the influences of the AVP hormone, which has a prominent role in cognitive functions like memory and learning (Fink et al. 2007). AVP has been shown to affect in different social (Thompson et al. 2004), emotional (Hammock 2007; de Boer et al. 2012) and behavioral (Donaldson & Young 2008; Knafo et al. 2008; Walum et al. 2008) traits, e.g. on male pair bonding and aggression (Thompson et al. 2004; Walum et al. 2008), parenting (Hammock & Young 2006), sibling relationships (Bachner-Melman et al. 2005) and altruism (Knafo et al. 2008.). In animal studies, *AVPR1A* has shown to be associated with social preferences of chimpanzee (Hopkins et al. 2012) and voles (Hammock 2007). Music's ability to attach individuals together and the property to add group cohesion is evident (Peretz 2006). Music collects masses of people to concerts and festivals. Playing music does not only bond individuals playing it together but also individuals listening to it. We and others have associated music related traits, namely musical aptitude, creativity in music (Ukkola et al. 2009), listening to music (Ukkola-Vuoti et al. 2010, creativity in music and musical memory (Granot et al. 2007), with polymorphisms of *AVPR1A* gene. These results support the claim that music is related to social communication (Perez et al. 2006) and it is linked to the same phenotypic spectrum of human cognitive social skills like bonding (Walum 2008). This being said, we do note that musical aptitude is a complex phenotype affected by several predisposing genes and environment, and thus this result, although interesting, is preliminary and may only partially explain the genetic background of musical aptitude.

5.3. Genome-wide copy number variations (CNVs) in musical aptitude (III)

After the first candidate gene studies, genome-wide data of the study sample was obtained in 2011. The genome-wide copy number variations (CNVs, see 2.2.2) in musical aptitude were analyzed using a SNP-panel of over 700,000 SNPs. Five extensive pedigrees (Appendix I, family no. 6, 13, 14, 15 and 17) and 172 unrelated subjects characterized for musical aptitude and creative functions in music were chosen for the study (III). Only the largest of the families were chosen for the study as they enabled the segregation analysis of the CNVs.

Several CNVRs containing genes that affect neural migration, differentiation, synaptogenesis, learning, memory and neurodevelopmental disorders were detected. A total of 67 % of the high music test scoring family members in families 6 and 14 carried a deletion at 1q21. The region has previously been linked with schizophrenia, autism, ADHD, learning disabilities, intellectual disability and dyslexia (Stefansson et al. 2008; Grayton et al. 2012). A deletion at 5q31.1 covering the protocadherin-α gene cluster (*PCDHA 1-9*) was found from 54 % of the low music test scoring participants in families 14 and 15. *PCDHA* genes are involved in neural migration, differentiation and synaptogenesis (Katori et al. 2009). A duplication covering the glucose mutarotase gene *(GALM)* at 2p22 was found from 27 % of the subjects reporting creative functions in music reporting subjects. *GALM* has been previously associated with serotonin transporter binding potential of the human thalamus (Djurovic et al. 2009). Thalamus is also important region for music perception process (Koelsch & Siebel 2005). *GALM* has influence on serotonin release and membrane trafficking of the serotonin transporter (Djurovic et al. 2009). *PCDHA* and *GALM,* are related to the serotonergic systems influencing cognitive and motor functions, and as such likely are important for music perception and practice. Previously, abnormalities in learning and memory were seen in *Pcdha* mutant mice (Fukuda et al. 2008). These functions are important for music perception and practice as well. Thus, *PCDHA* and *GALM* are plausible candidate genes for music perception and practice. Further, associations of serotonin transporter gene (*SLC6A4*) together with arginine vasopressin receptor gene (*AVPR1A*) polymorphisms with artistic creativity in professional dancers (Bachner-Melman et al. 2005) and with short-term musical memory (Granot et al. 2007) support our results.

Large CNVs were detected in some of the study participants. A 1.3 Mb long duplication in the core linkage region of previous AP study (rs755520-rs2102861) at chromosome 8q24 (Theusch et al. 2009) was detected in a subject with low COMB scores. The region contains gene *ADCY8* (adenylate cyclase 8) which is related to synaptic plasticity, short-term memory performance (Wong et al. 1999) and bipolar disorder (Zhang et al. 2010). Further, a 2.1 Mb long duplication at 15q26, containing schizophrenia susceptibility gene multiple C2 domains, transmembrane 2 (*MCTP2),* is transmitted in a family in three generations (Figure 14). Over 1 Mb CNVs are known to occur in 1-2 % of healthy individuals (Redon et al. 2006; Pinto et al. 2007; Conrad et al. 2010; Dauber et al. 2011; Yeo et al. 2011).

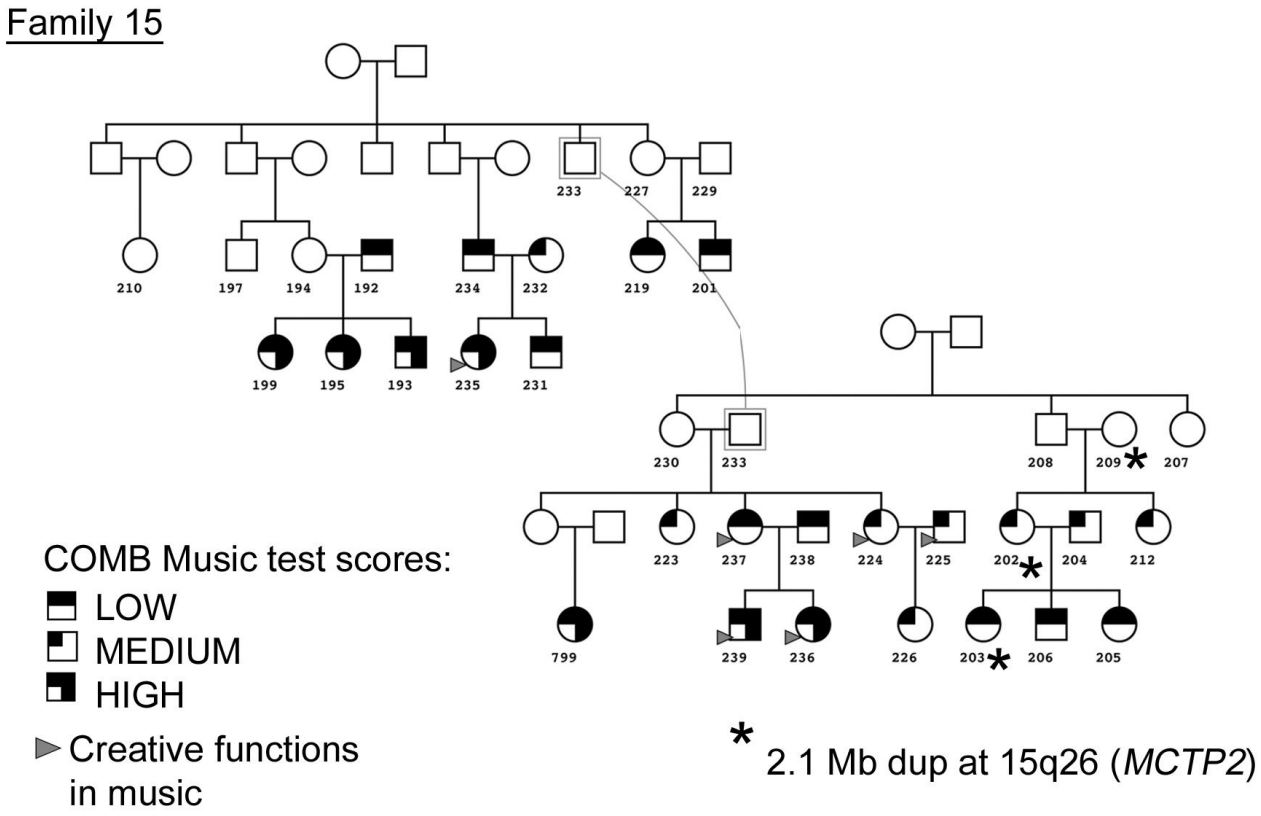


Figure 14. A large duplication at 15q26 was transmitted in three generations in family no.15. The region contains schizophrenia susceptibility gene *MCTP2* multiple C2 domains, transmembrane 2. COMB= combined music test scores, LOW= <105.0, HIGH= >137.0, dup= duplication. Circles illustrating females, squares males and ID-numbers of each family member are under the symbol.

Previously, Girirajan et al. (2011) showed positive correlation between large CNV burden and severity of neurodevelopmental disabilities (autism and intellectual disability) while the CNV burden in less severe phenotype, dyslexia, could not be distinguished from controls. In the study III, no differences in the CNV burden was detected among the high/low music test scores or creative/non-creative groups. The phenotypes studied here cannot be considered as disabilities, thus our result is in agreement with previous studies.

We found the family approach useful, as we could obtain evidence for inherited CNVs, better control of population stratification and enrichment of rare variants (Antoniou & Easton 2003). At present, algorithms used in this study (PennCNV and QuantiSNP) constitute the most reliable set-up for Illumina SNP platform based CNV detection (Dellinger et al., 2010). Still, one has to keep in mind that the detection techniques with the existing algorithms are far from being comprehensive (Dellinger et al. 2010; Pinto et al. 2010; Pinto et al. 2011): many CNVs considered *de novo* have actually been transmitted from a parent, and *vice versa*.

Intelligence is sometimes considered as one division of creativity (Reuter et al. 2006). In this study, we did not detect any CNVs in the regions containing candidate genes of intelligence. Finally, the genome wide CNV analysis carried out here adds our general knowledge about CNVs in the healthy population.

5.4. Genome-wide scan of creative functions in music (IV)

Genome-wide association study of creative functions in music was performed with enlarged family material comprising of a total of 92 families with 412 family members (IV). Of the participants, 29 % reported to practice creative functions in music. Several regions of the genome showed association with creative functions in music. The strongest associated region was found at chromosome 10q21 with three associated SNPs. Two of the SNPs located in the introns of the protein kinase cGMP-dependent type I (*PRKG1*) gene ($p = 9.1x10^{-7}$ and $p = 3.64x10^{-5}$, respectively) and one suggestively associated was intergenic ($p = 3.82x10^{-5}$, respectively). *PRKG1* is expressed in the amygdala and suggested to support synaptic plasticity, neuronal growth, learning and memory. Brain imaging studies have shown that the amygdala is active in the improvising musician (Liu et al. 2012). Further, music has shown to induce neuroplasticity (Jenkins et al. 1990; Recanzone et al. 1993; van Praag et al. 2000; Kilgard et al. 2001); grey and white matter volume is greater in the individuals who have learned music in the early ages (Munte et al. 2002) and active training in and practising of music has been shown to enlarge some areas of the brain (Elbert et al. 1995).

Further, an intronic SNP of the ras protein-specific guanine nucleotide-releasing factor 2 (*RASGRF2*) gene was tentatively associated with creative functions in music (best p-value $1.31x10^{-5}$). Notably, also in our genome wide CNV screen deletion in the region covering *RASGRF2* was related to creative functions in music. Intriguingly, Xiang and colleagues (2012) associated both *PRKG1* and *RASGRF2* with memory dysfunction in schizophrenia.

In music, creativity is a complex cognitive function of the brain, a powerful tool forming the basis for music culture and music industry. In our studies composing, improvising and arranging music exhibit creative functions in music. The brain imaging studies on musicians have shown that various brain regions activate while improvising. These regions include cortical, neocortical and prefrontal regions, the left posterior part of the superior temporal gyrus (Bengtsson et al., 2007; Berkowitz & Ansari 2008; Limb & Braun 2008), medial and dorsolateral prefrontal corticles, medial prefrontal, cingulated motor, perisylvian corticles and amygdala (Liu et al. 2012). In this study, the *PRKG1* gene which is expressed in the amygdala (Paul et al. 2008) was indicated. Expression of the identified genes previously linked to

neuropsychiatric conditions in the regions where music is perceived may suggest that same susceptibility genes and molecular pathways are contributing to creativity in music and neuropsychiatric disorders. One must however note that the specific polymorphisms in these genes need not be the same ones affecting both special abilities and neuropsychiatric disabilities. Having that said, the relationship between creativity and madness has been under discussion since ancient times. Based on biographies on creative artists creativity and psychopathology have been described in the same person. In the face of evolution creativity is a necessary and useful trait whereas neuropsychiatric disorders can be harmful. In spite of their destroying effects on human mind neuropsychiatric disorders have persisted in evolution suggesting that they perhaps also carry an advantageous effect on evolution (Kyaga et al., 2011). During the last years, some evidence for common molecular background of psychiatric diseases and creativity has been reported also by others: Keri 2009; Belsky et al. 2009; Kyaga et al. 2011. Both dopamine and serotonin transporters have been suggested to associate with creativity and psychiatric disorders (Reuter et al. 2006; de Manzano 2010; Carson 2011). Bipolar disorder is more common among relatives of creative subjects (Kyaga et al. 2011). Thus, a connection between genes contributing to human creativity, a high-level function of the brain and neuropsychiatric disorders has been suggested. Risk alleles associated with psychiatric diseases have been shown to affect brain plasticity.

Previously, only a limited number of genetic studies, including candidate gene studies of creative dance (Bachner-Melman et al, 2005), musical memory (Granot et al. 2007), choir singing (Morley et al. 2012), and genome-wide analyses of musical aptitude (Pulli et al. 2008), pitch production accuracy (Park et al. 2012) and absolute pitch (Theusch et al. 2009) have been performed in music related phenotypes. All these studies have indicated that music perception and practice have molecular genetic background.

6. CONCLUDING REMARKS AND FUTURE PROSPECTS

Music perception and performance are comprehensive cognitive functions and thus provide an excellent model system for studying human behavior and brain function. The hypothesis of this study was that music perception is an innate biologically determined trait that is affected by the environmental factors such as exposure to music stimuli. Molecular and statistical genetic approaches and bioinformatics were applied to investigate the biological background of music perception and related phenotypes, such as creative functions in music and listening to music.

Music perception was defined here as musical aptitude that represents a complex phenotype. The results of the heritability analyses suggest that the tests used here do measure genetic contribution to musical aptitude. A family based approach was adopted in this study to maximize the genetic homogeneity and to minimize the confounding factors. The advantages of the family-based study setting over population-based includes better control of population stratification, enrichment of rare variants and the ability to discriminate variants co-segregating with the trait (Antoniou & Easton 2003; Norio 2003).

The molecular genetic results obtained here suggest that musical aptitude and creativity in music are likely to be regulated by several predisposing genes or variants. Based on the results obtained in this study, creative functions in music are affected by different predisposing genetic variants than musical aptitude. In the genome wide copy number variation and SNP analysis several genes and genetic variants were detected that are affect brain function.

Being aware that musical aptitude is a complex phenotype affected by several predisposing alleles, environment and the interplay between them, the result, although interesting, is preliminary and may only partially explain the genetic background of musical aptitude. A number of unanswered questions still remain. The future studies including RNA and microRNA profiling after listening to music in different phenotypes related to music perception and practice will give some answers about the mutual crosstalk between genetic variants and environmental factors, into the development of musical aptitude. These questions

are of wide interest in the society that concern not only molecular genetics and neuroscience, but also brain diseases, music education and music therapy.

7. ACKNOWLEDGEMENTS

This study was carried out at the Department of Medical Genetics, Haartman Institute, University of Helsinki, during the years 2007-2012. Previous and current heads of the Department are acknowledged for providing excellent research facilities. My study was financially supported by the Research Foundation of the University of Helsinki, the Paulo Foundation, the Finnish Concordia Fund and the Miina Sillanpää Foundation. Other main supporters of the project were the Finnish Cultural Foundation, the Academy of Finland and the Biocentrum Helsinki Foundation.

I thank my supervisors, docents, Irma Järvelä and Päivi Onkamo. Together you have formed a perfect combination of knowledge and balanced each other well. Irma, I admire your passionate attitude towards inherited diseases and traits and the energy you are having 24/7. Päivi, I value your knowledge on statistics, aim for perfect quality research, understanding, cheerful company and the ability to bring some of our too creative ideas down-to-earth.

I wish to thank Professor Kari Majamaa for accepting the role of the Opponent in my thesis defence. Also, I am thankful for Professor Elena Maestrini and docent Rainer Lehtonen for reviewing this thesis and for their constructive and valuable suggestions to improve the manuscript.

I am deeply grateful to all co-authors and collaborators of this study. Without them this work would not have been possible. Docent Kai Karma and Dr. Pirre Raijas are thanked for their expertise in music and collecting part of the data. To Pirre I am also grateful for her warm support throughout this work and reviewing the music parts of my thesis. Maija Puhakka is thanked for secretarial assistance and other valuable support.

I wish to thank all the families who participated in this study.

I thank former and current members of Irma's research group. The colleagues Katri Kantojärvi, MSc, Jaana Oikkonen, MSc and Fatma Doagu, MSc, are thanked for creating good atmosphere in our office and for the (loud) discussions during the years. Special thanks to Katri for friendship and sharing both joy and pain during our PhD works. I am grateful to

the most polite colleague Chakravarthi Kanduri for his valuable work considering bioinformatics. Minna Varhala, RN, is thanked for being responsible for blood samples in numerous recruitments. Minna Ahvenainen, MSc, is acknowledged for language revision of this thesis and for technical help in the lab. The former inhabitant of our office, Inkeri Lokki, MSc, is thanked for constructive discussions.

I thank the Hawaii group Martin, Tarja, Katri and Päivi for the Hawaii and palju nights.

I want to thank all my friends. Special thank goes to Saija, Merja and Maija for the relaxing, memorable (and also for those not so memorable) moments during this work. Friends from Oulu are thanked. Sighthound people in Finland and abroad are thanked for helping through both victorious and sad moments. Family Pylkkänen is thanked.

Last but not least I thank my family for the everlasting support. My parents Raisa and Heino are thanked for all. My brother Marko is thanked for a helping hand and a listening ear. My husband Sauli is thanked for love and sharing his life with me. I am thankful for him to take good care of our house when I had too much work to do and for wise advices I got during this work. Kukka is thanked for for being the best company, the best racer and the best listener one can have. Unelma is thanked for being the sweet lapdog during the writing process and Vili for being born not sooner than at the end of the work.

Vantaa, April 2013.



8. ELECTRONIC DATABASE INFORMATION

The homepage of the research group and samples of the KMT, http://www.hi.helsinki.fi/music/

Ensembl Genome Browser, http://www.ensembl.org/index.html

FBAT/HBAT, http://www.hsph.harvard.edu/fbat/fbat.htm

Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim

QTDT, http://www.sph.umich.edu/csg/abecasis/QTDT/

R-program, http://www.r-project.org

UCSC Human Genome Browser, http://genome.ucsc.edu/

Primer3Plus, http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi/

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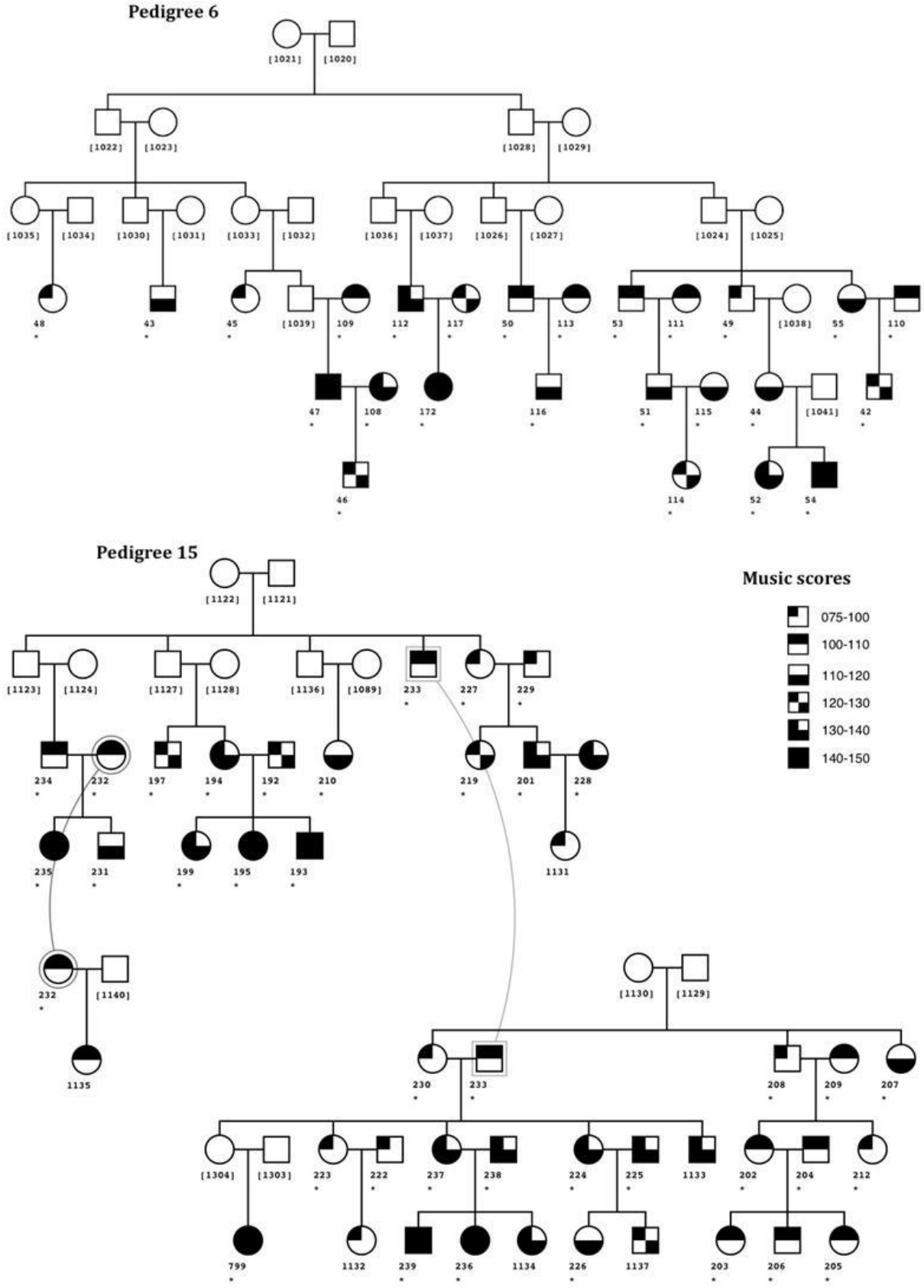
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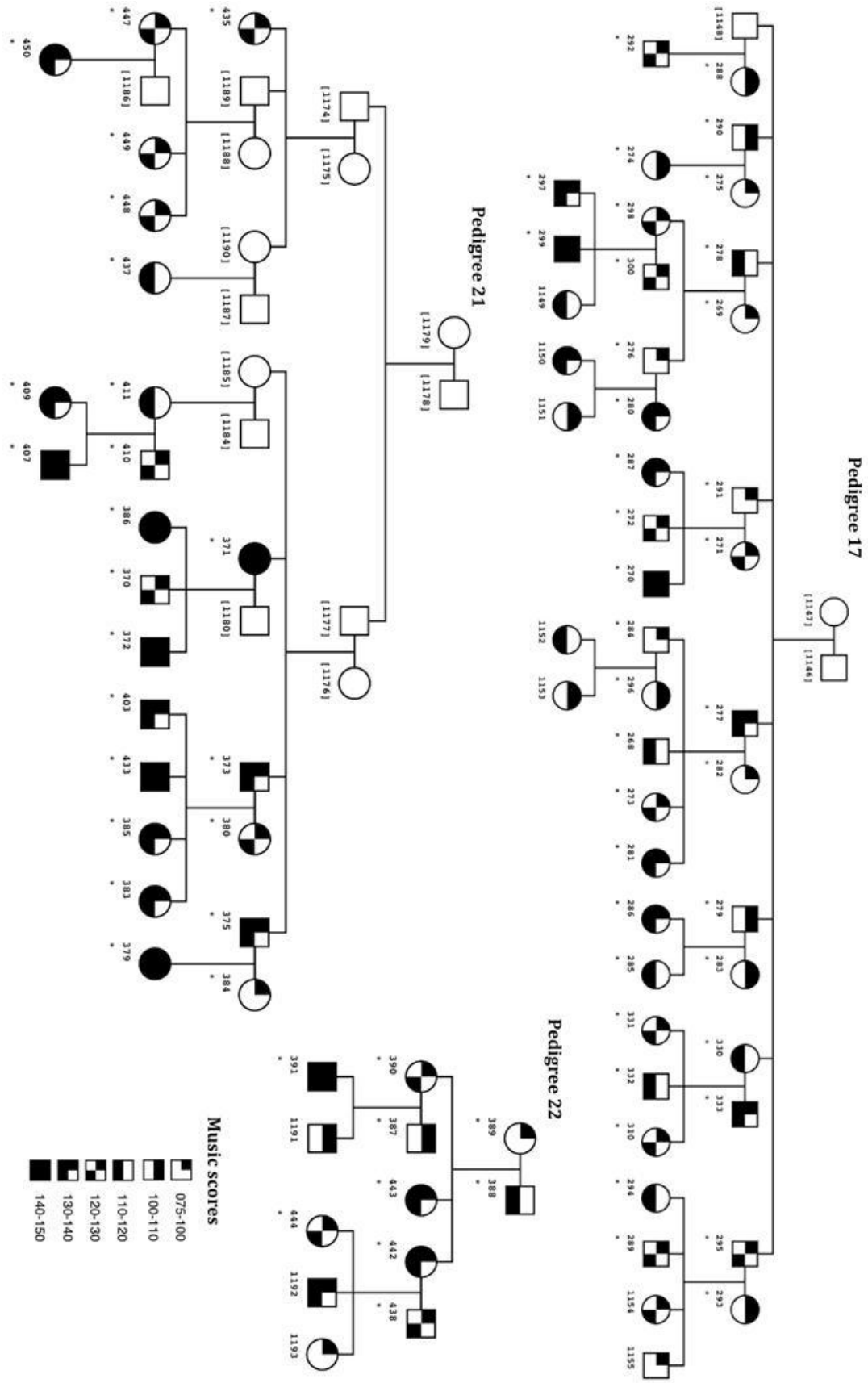
Appendix I: Examples of pedigrees from three different recruitments

Examples of pedigrees from each of three recruitment stages are shown in the following figures. The largest of the collected families and some other families are included in the figures. The pedigrees are drawn with the Cranefoot program (www.finndiane.fi/software/cranefoot/). Circles are illustrating female, squares male. Music test scores (COMB) are shown as patterns and available DNA as an asterisk (*) under the individuals. Individuals who have not attended the study (empty individuals) are marked with brackets. Curved links between two nodes assign for same individual who has been drawn twice.

Recruitment I.



Recruitment II.



Recruitment III.

