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The Molecular Genetic Basis of Music Ability and Music-Related Phenotypes

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AUTHOR NOTE

The chapter is adapted from the first author's doctoral dissertation (Tan, 2016). Readers are encouraged to refer to the thesis for further information.

INTRODUCTION

In the past decade, researchers have sought to uncover potential genes that underlie various musical traits through molecular genetic approaches once the genetic basis of a musical trait has been established using behavioral genetic methods. Since the 1980s, progress in molecular genetic technology and bioinformatics has brought about the advent of human molecular genetic approaches, especially for elucidating the genetic mechanisms of complex diseases. In contrast, the investigation of the molecular genetic basis of music ability only began to surface in recent years, with Järvelä and her collaborators contributing a sizeable and significant research output on this topic. Although this field is still in its infancy, some exciting and converging results are already beginning to emerge.

This chapter provides an overview of the main findings from molecular genetic studies on musical traits, which are broadly organized according to the categories shown in Table 1.

Table 1. The Number of Molecular Genetic Studies Investigating Various Music-Related Phenotypes

Category	Music subskill	No. of studies	Authors

Music perception	Basic music perception abilities	2	Pulli et al. (2008); Oikkonen et al. (2014)
	Higher level music perception abilities	6	Alcock et al. (2000); Pulli et al. (2008); Ukkola et al. (2009); Ukkola-Vuoti et al. (2013); Oikkonen et al. (2014); Liu et al. (2016)
	Music memory	2	Granot et al. (2007); Granot et al. (2013)
	Music listening	2	Ukkola-Vuoti et al. (2011); Kanduri, Raijas, et al. (2015)
	Absolute pitch	4	Theusch, Basu, & Gitscher (2009); Theusch & Gitschier (2011); Gregersen et al. (2013); Gervain et al. (2013)
Music production	Music performance	1	Kanduri, Kuusi, et al. (2015)
	Music creativity	3	Ukkola et al. (2009); Ukkola-Vuoti et al. (2013); Oikkonen et al. (2016)
	Singing participation	1	Morley et al. (2012)
	Singing accuracy	1	Park et al. (2012)
	Rhythm production	1	Alcock et al. (2000)
Music culture		2	Pamjav et al. (2012); Brown et al. (2013)

MUSIC PERCEPTION

As shown in Table 1, a majority of the molecular genetic studies have focused primarily on traits pertaining to music perception – the perception of musical pitches, melodies and rhythms, music listening behavior, and the uncommon music perception ability of Absolute Pitch (AP). These molecular genetic findings for each of these traits are discussed in the sections below.

Basic Music Perception Abilities

Possible genetic substrates underlying basic music perception abilities have been investigated by Järvelä and her collaborators in several large molecular genetic studies (Oikkonen et al., 2014; Pulli et al., 2008). In these studies, basic music perception abilities were measured using the pitch and time tests from the Seashore Measures of Musical Talents, in which participants were asked to detect differences in the pitch and note duration of 50 paired tones (Seashore, Lewis, & Saetveit, 1960).

Genome-wide linkage analysis revealed some evidence of linkage on chromosome 10 (LOD = 1.67) for pitch discrimination, and on chromosome 4q (LOD = 1.18) for note duration discrimination (Pulli et al., 2008). A subsequent larger-scaled genome-wide linkage and association study (Oikkonen et al., 2014) has also found evidence that chromosome 4 was implicated in music perception. For pitch discrimination, the best linkage was obtained at 4p14, with some evidence of linkage also observed at 22q11.21. In addition, the region 3q21.3 was associated with pitch and note duration discrimination. Interestingly, some of these implicated chromosomal loci contain genes that are expressed in the auditory pathway. For instance, the *PCDH7* gene is located next to 4p14, and is known to be expressed in the developing cochlea of chicken and the amygdala of mice (Hertel, Redies, & Medina, 2012; Lin et al., 2012), which provides tentative evidence for the gene's role in music perception and music-evoked emotions. On the other hand, located close to 3q21.3 is the *GATA2* transcription factor, which likely plays an important role in the development of cochlear hair cells and the inferior colliculus (Haugas, Lilleväli, Hakanen, & Salminen, 2010). The inferior colliculus is a core structure in the peripheral auditory pathways for music perception, supporting the initial integration of pitch, direction, and loudness information (McLachlan & Wilson, 2010). Moreover, *GATA2* is expressed in dopaminergic neurons (Scherzer et al., 2008), which release dopamine during pleasure-evoking activities such as music listening and performance (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011). Finally, the region 22q11.21 is linked to DiGeorge syndrome (also known as 22q11.2 deletion syndrome), which typically includes symptoms of conductive and sensorineural hearing losses (Digilio, Marino, Capolino, & Dallapiccola, 2005).

Higher Level Music Perception Abilities

The abilities to perceive tonal or rhythmic structures in music are more cognitively advanced forms of music perception than the pairwise discrimination of pitches or note durations. Because of this, Järvelä's research team has also investigated the ability to discern melodic and rhythmic patterns (referred to as auditory structuring ability) using the Karma Music Test (KMT) in two family pedigree studies (Oikkonen et al., 2014; Pulli et al., 2008). In the earlier study, genome-wide linkage analysis revealed promising evidence of linkage at 4q22 for the KMT (LOD = 2.91) and significant evidence of linkage (LOD = 3.33) for the combined score of the KMT and Seashore's pitch and time tests (Pulli et al., 2008). The subsequent genome-wide linkage and association study also found some evidence of linkage for 4q21.23–22.1 and 4q24 being linked to the KMT (Oikkonen et al., 2014). A possible candidate gene at 4q22 is the netrin receptor *UNC5C*. Netrins are responsible for directing axon extension and cell migration during neural development, with studies demonstrating interactions between netrins and robo family receptors (Stein & Tessier-Lavigne, 2001). One such receptor, *ROBO1*, is a candidate gene for dyslexia (Carrion-Castillo, Franke, & Fisher, 2013). Such results indicate possible shared molecular substrates between music and language, an assertion that is further strengthened by previous behavioral findings demonstrating that the KMT significantly predicts dyslexia (Karma, 2002).

Oikkonen et al.'s (2014) genome-wide linkage and association study has also found potential linkage evidence for the KMT at 16q21-22.1, which overlaps with a previously proposed hearing impairment locus (Basit et al., 2011). Furthermore, association analysis conducted in this study revealed that the KMT was associated with 5q31.3, 1p31.1, and 11q21. While the association at 1p31.1 and 11q21 was not linked to any known gene near these loci, the gene *NDFIP1* is located at 5q31.3 and has a function in immune signaling regulation (Wang, Tong, & Ye, 2012). In addition, this study also revealed that some of the chromosomal regions showing evidence of linkage for the combined score (KMT and Seashore’s pitch and time tests) contain genes implicated in the auditory pathway. For instance, the linked region 18q12.3-21.1 contains the gene *LOXHD1* which is expressed in the inner ear hair cells and results in auditory defects in the case of mutation (Grillet et al., 2009). In another linked region, 4p12-q12, the gene *PDGFRA* is expressed in the cochlea of mice (Ballana et al., 2008), and the gene *KCTD8* is expressed in the spiral ganglion, a group of nerve cells in the cochlea.

In a genome-wide copy number variation (CNV) analysis, Järvelä and her collaborators detected several copy number variable regions containing genes that influence neurodevelopment, learning, and memory (Ukkola-Vuoti et al., 2013). Notably, a deletion on 5q31.1 was present in some participants with a low combined score on the KMT and Seashore’s pitch and time tests. This particular region covers the protocadherin-α gene cluster (*Pcdha 1-9*), which is involved in the synaptogenesis and maturation of serotonergic projection neurons, as well as learning and memory (Fukuda et al., 2008). The authors proposed *Pcdha* as a plausible candidate for music perception since learning and memory are important for music perception and the development of musical expertise (McLachlan, Marco, Light, & Wilson, 2013). Also noteworthy is the identification of a large duplicated region on 8q24.22 in an individual with a low combined score, which happens to overlap with a major linkage region for AP (Theusch, Basu, & Gitschier, 2009). Thus, duplication in the putative AP linkage region may have a negative impact on pitch perception, since large duplications are known to be potentially detrimental to neurodevelopment (Almal & Padh, 2012).

Extending these findings, a candidate gene study by Järvelä and her team has demonstrated significant associations between the haplotype RS1 and RS3 of the *AVPR1A* gene on chromosome 12q and the combined score for the KMT and Seashore’s pitch and time tests (Ukkola, Onkamo, Raijas, Karma, & Järvelä, 2009). Arginine vasopressin (AVP) has previously been implicated in social cognition and behavior (Bielsky, Hu, Szegda, Westphal, & Young, 2004; Ferguson, Young, & Insel, 2002) and in social and spatial memory (Aarde & Jentsch, 2006; Ferguson et al., 2002). Its association with auditory structuring ability therefore suggests a potential link between music perception and human social functioning.

Recently, Järvelä's team conducted a genome-wide positive selection analysis on the music perception ability of 148 Finnish participants, as measured by the combined score for the KMT and Seashore's pitch and time tests (Liu et al., 2016). Using a case-control design (cases: > 125/150 for combined score vs. controls: < 117.25/150 for combined score; as determined from the residuals of a fitted linear regression between the combined score and age of participants), these researchers identified numerous chromosomal regions that show differential positive selection signals between cases and controls using several haplotype-based and frequency-based selection methods. Because a large number of positive selection regions were identified, it was difficult to interpret the functional importance of these regions. As such, the researchers described in detail only the genes important in brain function, hearing, and the singing network of songbirds.

Several genes found within the positive selection regions are involved in inner-ear development and auditory perception. *GPR98* at 5q14.3, for example, is necessary for proper development of auditory hair bundles (McGee et al., 2006) and has a possible function in birdsong (Pfenning et al., 2014). *USH2A* at 1q32.3-41 is also required in the development of cochlear hair cells, which influence hearing sensitivity (Liu et al., 2007). Both *GRP98* and *USH2A* have also been associated with Usher syndrome, which includes symptoms of deafness. These findings are in line with an earlier molecular genetic study on music perception ability which implicated genes associated with inner-ear development and cognition (Oikkonen et al., 2014). Some genes found within the positive selection regions were also implicated in cognition and memory. For instance, *GRIN2B* at 12p13.1 is involved in learning and neural plasticity in the temporal lobe (Milnik et al., 2012). It is also one of the expressed genes in the singing control network of the zebra finch (Pfenning et al., 2014). Moreover, *IL1B* at 2q14 is linked to cognition and working memory (Benke et al., 2011) and *RAPGEF5* at 7p15.3 may also have implications for learning and memory (Ostroveanu, Van Der Zee, Eisel, Schmidt, & Nijholt, 2010). On the other hand, one of the selection regions contains *GZMA* (at 5q11.2), a gene associated with neurodegeneration that has previously been noted to be downregulated after music listening (Kanduri, Raijas, et al., 2015).

The study by Liu et al. (2016) also reported that the positive selection region on chromosome 17 contained the *RGS9* gene (17q24). One variant of the gene (*RGS9-2*) is putatively associated with reward mechanisms because it interacts with dopamine receptors in the striatum (Taymans, Leysen, & Langlois, 2003). This finding is in keeping with previous studies that have noted an association between dopamine release and music-induced reward (Salimpoor et al., 2011). Another gene from the RGS family, *RGS2*, which was reported to be upregulated after performing and listening to music (Kanduri, Kuusi, et al., 2015; Kanduri, Raijas, et al., 2015), has also been previously implicated in the vocal learning of songbirds. Thus, this research suggests that RGS proteins may be potential candidate genes for the evolution of music. In fact, approximately 5% of the identified candidate genes (e.g. *FOXP1*, *RGS9*, *GRIN2B*, *GPR98*, *VLDLR*) in the positive selection regions are related to song perception and production in songbirds (Pfenning et al., 2014), which suggests a possible cross-species evolutionary conservation of genes associated with auditory perception. Among these candidate genes, *FOXP1* at 3p13 and *VLDLR* at 9p24.2 are also known to be involved in language development (Chen, Heston, Burkett, & White, 2013), pointing to a possible common genetic and evolutionary background for music and language.

As for a possible genetic substrate underlying rhythm perception, the study of a three-generation family pedigree (KE family) with multiple probands of severe speech and language disorder has shown that the affected individuals also demonstrated an impairment in rhythm perception and production, while their pitch perception and production abilities remained intact (Alcock, Passingham, Watkins, & Vargha-Khadem, 2000). Subsequent gene sequencing has demonstrated that the affected KE family members has a point mutation in the *FOXP2* gene (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). Taken together, these findings suggest a possible shared genetic basis for speech and rhythm, in contrast to pitch-based music abilities which seem likely to be influenced by other genetic factors (Peretz, 2009).

Music Memory

Granot and colleagues (2007) have investigated the possible association of phonological and music memory with the genes *AVPR1A* and *SLC6A4*. The grounds for interest in this association come from previous research indicating a possible epistatic relationship between *AVPR1A*, which is a receptor for AVP, and *SLC6A4*, a serotonin transporter (Albers, Karom, & Smith, 2002), in addition to the association of AVP with spatial and social memory (Aarde & Jentsch, 2006; Ferguson et al., 2002). In this study, 82 university students with minimal music training were genotyped for the *AVPR1A* (RS1 and RS3 haplotypes) and the *SLC6A4* (HTTLPR) polymorphisms using population-based and family-based association analyses. The music memory performance of the participants was assessed using four melodic memory tests and two rhythmic memory tests. Results revealed significant gene-by-gene epistatic interactions between the *AVPR1A* and *SLC6A4* polymorphisms for two of the melodic memory tests (the Gordon melodic imagery subtest from the Musical Aptitude Profile, and the interval subtest from the Montreal Battery of Evaluation of Amusia [MBEA]), one of the rhythmic memory tests (Seashore's rhythm perception task), and one phonological memory task. These results remained robust even after applying conservative Bonferroni corrections for multiple testing. They provide initial evidence for an epistatic relationship between *AVPR1A* and *SLC6A4* polymorphisms that may be linked to short-term memory for music, or more generally, to phonological memory.

In a follow-up study, AVP was administered intranasally to 50 male adults with little or no music training in a double-blind, placebo-controlled, crossover study (Granot, Uzefovsky, Bogopolsky, & Ebstein, 2013). At the end of each session (AVP/placebo), the participants' music working memory was assessed using the melodic imagery subtest from Gordon's Musical Aptitude Profile and the interval subtest from the MBEA, while verbal working memory was assessed with digits forward and backwards from the Digit Span task. Although AVP administration was not found to affect digit span performance significantly, a complex pattern emerged for the music memory tasks. Specifically, for the MBEA test, in both sessions, the group that received AVP first performed more poorly than the group that received the placebo first. For Gordon's melodic imagery subtest, both groups performed significantly better in the second session, with the group that received placebo first marginally outperforming those who received AVP first. Findings also showed that for the group who received AVP first, their music memory scores were significantly positively correlated with their affective state scores. On the basis of these findings, the researchers argued that the apparent detrimental effects of AVP on music memory may be mediated by mood, attention and arousal, such that only those who scored low on happiness and attentiveness were negatively affected by AVP in terms of their music working memory. In light of music's propensity for modulating arousal and AVP's influence on mood and arousal, the researchers deemed it conceivable that the documented associations between AVP and music perception, creativity, and memory might reflect individual differences in arousal and attention modulation rather than individual differences in cognitive or social abilities per se.

Music Listening

Listening to music is a prevalent behavior in all known human cultures. To investigate this human attribute, Järvelä's team examined the role of *AVPR1*a gene polymorphisms in the active and passive music listening behavior of 31 Finnish families using family-based association analysis (Ukkola-Vuoti et al., 2011). Findings indicate that current active music listening was significantly associated with the RS1 and AVR haplotype, whereas lifelong active music listening was significantly associated with the RS1 and RS3 haplotype. A possible shared genetic basis for the frequency of lifelong active music listening and music perception ability was proposed by the authors, given that the same haplotype (RS1 and RS3) was previously demonstrated to be associated with music perception (Ukkola et al., 2009). Given the well-established role of AVP in mediating social behavior (Bielsky et al., 2004), the researchers proposed that these findings provide tentative evidence that music listening may share common neurobiological substrates with social attachment and communication.

The above research has been extended to investigate the effect of listening to classical music on human transcriptome using genome-wide transcriptional profiling (Kanduri, Raijas, et al., 2015). It was found that in participants with high musical experience (based on years of music training or music perception ability), several genes implicated in dopamine secretion, transport, and signaling were upregulated, converging with previous evidence that showed that music listening induces dopaminergic release and transmission (Salimpoor et al., 2011). Notably, one of the most upregulated gene *SNCA* is a known risk gene for Parkinson's disease (Scherzer et al., 2008), and is located on the most significant linkage region for music perception ability, 4q22.1 (Oikkonen et al., 2014; Pulli et al., 2008). In addition, *SNCA* is regulated by *GATA2*, a transcription factor which has a possible association with music perception ability (Oikkonen et al., 2014). Other upregulated genes in participants with high musical experience included those associated with learning, memory and cognition (e.g. *SNCA*, *NRGN*, *NPTN*), synaptic function and neurotransmission (e.g. *SNCA, HDAC4*, *FKBP8*), neuroprotection and neurogenesis (e.g. *SNCA*, *KLF4*), and auditory cortical activation and absolute pitch (e.g. *FAM49B*, *HDAC4*). Importantly, some of the upregulated genes (e.g. *SNCA*, *NRGN*, *RGS2*) are also known to be associated with song perception and production in songbirds (Wada et al., 2006), suggesting a potential cross-species shared evolutionary background for sound perception. On the other hand, several of the downregulated genes (e.g. *ATP5J*, *ATP5L*, *GZMA*, *CASP8*) are involved in neurodegenerative processes. Collectively, the downregulation of genes implicated in neurodegeneration and the upregulation of genes involved in neurogenesis and neuroprotection indicate that music listening may have a neuroprotective role, supporting the use of music therapy in people with neurodegenerative diseases.

Absolute Pitch

Absolute pitch (AP) or "perfect pitch" is the rare musical ability of being able to identify or produce pitches without relying on an external reference tone. It has an estimated prevalence of less than 1 in 10,000 (Bachem, 1955), although more recent studies have suggested the prevalence could be closer to 1 in 1,500 (Profita & Bidder, 1988).

A genome-wide linkage study of 73 AP families (each with ≤ 2 AP possessors) of European, East Asian, Ashkenazi Jewish, and Indian descent in the United States and Canada revealed suggestive linkage evidence on chromosomes 8q24.21 (LOD = 2.33) and 8q21.11 (LOD = 2.07) for the European/Ashkenazi Jewish/Indian combined dataset (Theusch et al., 2009).

Notably, the gene *ADCY8* is located near the linkage peak on 8q24.21, which is expressed almost exclusively in the brain and is implicated in learning and memory processes (De Quervain & Papassotiropoulos, 2006). When only the subset of 45 European AP families was examined, there was strong evidence of linkage on 8q24.21 (LOD = 3.46) for AP, suggesting that genes such as *FAM49B* and *ADCY8* within this linkage region could potentially predispose individuals of European descent. Other linkage peaks were also found in the European AP families, namely on loci 8q21.11 (LOD = 2.24), 7q22.3 (LOD = 2.07) and 9p21.3 (LOD = 2.05). These peaks suggest that multiple genetic factors may underpin the etiology of AP, even within the same population. Interestingly, the linkage region on 7q22.3 was also observed in a subset of 19 AP families of East Asian ancestry, albeit with a smaller linkage peak (LOD ≈ 1-1.5). Taken together, these findings support a strong and possibly heterogeneous genetic contribution to AP, both within and across populations of different ancestries.

Another genome-wide linkage study investigated the genetic relationship between AP and synesthesia in 53 multiplex families with AP (i.e., families with multiple AP possessors) and 36 multiplex families with synesthesia (Gregersen et al., 2013). Notably, approximately 22% of the AP possessors from the AP families reported synesthesia, while eight synesthesia families also had AP possessors within each family. Non-parametric linkage analyses conducted separately on the AP and synesthesia datasets revealed overlaps in several linkage regions (LOD > 2), especially on chromosomes 2 and 6. Given this overlap and the hypothesis that the two phenotypes may be jointly influenced by genes underpinning brain structural and functional connectivity, the AP and synesthesia datasets were combined for further linkage analysis. Significant linkage evidence was found at 6q14.1-6q16.1 (LOD = 4.68), which coincided with the small linkage peak (LOD = 1.72) previously reported for AP families of European ancestry (Theusch et al., 2009). Upon sequencing several potential candidate genes in this region, Gregersen and colleagues found that AP possessors from four of the AP multiplex families shared one or more of three non-synonymous variants of the gene *EPHA7* at 6q16.1. *EPHA7* has been implicated in brain development, particularly establishing neural connectivity between auditory cortex and other cortical regions with the thalamus (Torii, Hackett, Rakic, Levitt, & Polley, 2013). Since neuroimaging studies have reported that both AP and synesthesia are marked by atypical structural and functional connectivity (Dovern et al., 2012; Rouw & Scholte, 2007), it is conceivable that *EPHA7* variants may underpin these two traits. A more complex pattern of linkage was also observed on chromosome 2 in the combined AP and synesthesia dataset, with a heterogeneity LOD score of 4.7 on 2q24.1. When only the AP families were considered, a maximum heterogeneity LOD score of 3.93 was observed on 2q22.1.

Apart from one documented case of a non-musically trained AP possessor (Ross, Olson, & Gore, 2003), most AP possessors report early onset of music training (Levitin & Zatorre, 2003), which suggests a possible critical time window for the development of AP. Previous studies have reported that the inhibition of *HDAC* (histone-deacetylase), an enzyme which serves as a “brake” to critical-period neuroplasticity, could reopen the critical window and alter music preference or enable recovery from amblyopia in adult mice (Silingardi, Scali, Belluomini, & Pizzorusso, 2010; Yang, Lin, & Hensch, 2012). Based on this evidence, Gervain et al. (2013) investigated whether the administration of valproate, a *HDAC* inhibitor may potentially reopen the critical period for AP development and facilitate pitch naming ability in 24 non-musically trained adult males. Using a randomized, double-blind, placebo-controlled crossover study, during each treatment arm, the participants took either valproate or placebo capsules over the course of 15 days and underwent daily 10-minute pitch association online training from days 8 to 14 before taking the AP assessment task on day 15. Results showed that in the first treatment arm, the valproate group performed significantly above chance level while the placebo group performed at chance. Intriguingly, in the second treatment arm, no significant difference in performance was observed between the two groups as both performed at chance level. It was suggested that the worse performance in both groups during the second treatment arm could be due to a memory conflict whereby the set of pitches learned in the first treatment interfered with those learned in the second treatment. The researchers therefore concluded that the significant findings from the first treatment arm offered a preliminary, proof-of-concept demonstration that valproate has an effect on AP perception, potentially by reactivating critical period learning through *HDAC* inhibition. It is important to note, however, that no significant correlation between AP performance and valproate levels in the blood was observed.

MUSIC PRODUCTION ABILITIES

Music Performance

Using genome-wide transcriptional profiling, Järvelä's research team have investigated the effect of performing music on the human transcriptome in 10 professional musicians (Kanduri, Kuusi, et al., 2015). Peripheral blood samples from the musicians before and after a 2-hour concert performance were compared to those of 10 musician controls before and after a 2-hour session without music exposure. Similar to their transcriptome study on music listening (Kanduri, Raijas, et al., 2015), music performance was observed to upregulate several genes involved in dopaminergic neurotransmission, one of which was *SNCA*, a gene on chromosome 4q22.1 previously identified as a strong candidate for music perception ability (Oikkonen & Järvelä, 2014; Pulli et al., 2008), music listening (Kanduri, Raijas, et al., 2015), and a possible early biomarker for Parkinson's disease (Scherzer et al., 2008). In addition, other motor behavior-related genes including *CCR4* and *FOS* were also upregulated, which may potentially shed light on the molecular mechanisms for executing music-related fine motor skills. Other upregulated genes included those implicated in learning and memory (e.g., *FOS*, *HDC*, *CLN8, DOPEY2*), and biological processes crucial for neuronal survival and neuroprotection, such as calcium ion and iron ion homeostasis (e.g., *SNCA*, *FOS*, *CLN8*).

It is noteworthy that this study also found that some genes known to be involved in song perception and production in songbirds (e.g., *SNCA*, *FOS*, *DUSP1*) were upregulated in music performance. This suggests a possible evolutionary conservation in sound perception and production molecular mechanisms. In addition, several of the upregulated genes such as *SNCA*, *FOS*, *CLN8* and *DOPEY2* have been implicated in neuropsychiatric or neurodegenerative disorders (Byun et al., 2013; Scherzer et al., 2008; Smith et al., 1997; Vantaggiato et al., 2009). The researchers therefore speculated that modulation of these genes by music performance may serve to explain music's therapeutic effects (Conrad, 2010).

Music Creativity

The genetic basis of music creativity was first investigated in a candidate gene study involving 19 Finnish musical families who were assessed using a web-based questionnaire. This consisted of questions about music background and participation in creative music activities, such as music composition, improvisation or arrangement (Ukkola et al., 2009). Findings suggest that creative functions in music have a strong genetic component, with a heritability estimate of .84 reported for this sample. While a significant positive association between music creativity and high music perception test scores was observed, no significant associations between music creativity and the polymorphisms of candidate genes such as *TPH1*, *COMT* and *AVPR1A* were found.

Ukkola-Vuoti et al. (2013) performed a subsequent CNV analysis on five multigenerational Finnish families and 172 unrelated individuals using the same music creativity questionnaire. A "creative phenotype" was characterized by engagement in at least one creative music activity (i.e., composing, improvising, or music arranging). Results showed that a deletion on 5p15.33 was present in 48% of family members and 28% of unrelated participants who exhibited the creative phenotype, while a duplication on 2p22.1 was present in 27% of the creative family members. On the other hand, deletions in three CNV regions (2p12, 3p14.1 and 3q28) occurred in 19% to 31% of family members who did not engage in creative music activities. The researchers speculated that the link between 2p22.1 and music creativity may be due to the gene *GALM* found at that locus, which is associated with serotonin transporter binding potential in the human thalamus (Liu et al., 2011). The medial geniculate nucleus of the thalamus forms part of the auditory pathways, and more generally has been implicated in music-related functions such as beat perception (McAuley, Henry, & Tkach, 2012), sensorimotor synchronization (Krause, Schnitzler, & Pollok, 2010), and musical imagery (Goycoolea et al., 2007). Other studies have also found a link between the serotonin transporter gene (*SLC6A4*) and music-related functions such as choir participation (Morley et al., 2012) and creative dance (Bachner-Melman et al., 2005).

Using an expanded version of their original questionnaire, the same Finnish research group recently performed genome-wide linkage analysis on a large sample consisting of 474 participants from 79 families and 103 unrelated individuals to investigate engagement in three forms of music creativity, namely, composing, arranging, and improvising (Oikkonen et al., 2016). The heritabilities for the various phenotypes estimated from the family data were moderate in general [composing: 33.3%; arranging: 33.4%; non-musically creative phenotype (defined as musically trained individuals who neither compose nor arrange): 28.9%], with the exception of improvising which had a low heritability estimate of 11.6%. The phenotypes with moderate heritability were then selected for genome-wide linkage analysis. For arranging, suggestive linkage evidence was observed at 16p12.1-q12.1 (LOD = 2.75), which is near the previously identified chromosomal region for music perception (Oikkonen et al., 2014). The best linkage evidence in the region was obtained at 16p12.1 (LOD = 4.22), in the intron of the *GSG1L* gene, which is implicated in fast synaptic transmission in the central nervous system (Shanks et al., 2012). Suggestive linkage evidence at 4q22.1 was found for composing (LOD = 2.15), which overlaps with the previously identified loci (4q22-23) for music perception ability (Oikkonen et al., 2014; Pulli et al., 2008) and is in the vicinity of the implicated locus (4q26) for vocal pitch-matching accuracy (Park et al., 2012). Furthermore, the locus 4q22.1 also contains the gene *SNCA*, which was previously observed to be one of the most up-regulated genes after music listening and music performance (Kanduri, Kuusi, et al., 2015; Kanduri, Raijas, et al., 2015). The converging findings therefore add credence to the chromosome 4 region being a candidate region for various music-related traits and point to a common genetic background for these traits. Functional analysis of putative genes in the implicated chromosomal region for composing indicated an overrepresentation of the cerebellar long-term depression (LTD) pathway: 17 out of the 141 known genes involved in the LTD pathway were found in the analysis for genes suggestively associated with composing. The LTD pathway is purportedly a cellular model for synaptic plasticity and memory (Collingridge, Peineau, Howland, & Wang, 2010), which are cognitive attributes arguably relevant to creatively composing music from existing knowledge structures. In addition, the LTD pathway contains the aforementioned *GSG1L* gene which is suggestively linked to arranging. This implies that individual differences in genes affecting the LTD pathway may potentially influence music creativity.

Interestingly, at 18q21, there was significant linkage evidence (LOD = 3.09) for the non-musically creative phenotype, with the best linkage evidence in the vicinity of the *CDH7* and *CDH19* genes from the cadherin family. These genes have been linked to neuropsychiatric conditions such as schizophrenia (Redies, Hertel, & Hübner, 2012), and *CDH7* is also implicated in the vocal development of songbirds (Matsunaga & Okanoya, 2008). The significant linkage region at 18q21 has also been associated with the 18q deletion syndrome which may cause hearing loss and intellectual disability, and is adjacent to a previously identified loci (18q23-21.1) for music perception ability (Oikkonen et al., 2014).

A major limitation of the above studies is that the creative phenotypes were not defined quantitatively by objective testing nor were they indicative of actual creative ability. Therefore, there is a possibility that these phenotypes may reflect a willingness or motivation to engage in music creativity rather than the actual ability itself. Furthermore, by defining the non-musically creative phenotype as musically-trained individuals who do not actively compose or arrange music appears to be dismissive of other manifestations of music creativity that do not involve composing or arranging. A more carefully considered characterization of various music creativity phenotypes is thus warranted.

Singing

Using a single note vocal pitch-matching task, Park et al. (2012) investigated the genetic factors underpinning singing ability by conducting family-based linkage and association analyses on 1,008 participants from 73 extended Mongolian families. Genome-wide linkage analysis revealed that the most significant linkage peak for singing accuracy was on 4q23 (LOD = 3.1), which overlaps with other regions on chromosome 4q implicated in music perception ability (Oikkonen et al., 2014; Pulli et al., 2008). The researchers also utilized exome sequencing to find other potential candidate SNPs and discovered a non-synonymous SNP (rs4148254) in *UGT8* on 4q26 that was significantly associated with singing accuracy. *UGT8* encodes *UDP* glycosyltransferase 8, a protein highly expressed in the brain (especially the substantia nigra) which catalyzes the transfer of galactose to ceramide. In addition, CNV analysis using an array comparative genomic hybridization (aCGH) platform has shown that a copy number loss at 5.6kb (5,600 base pairs) upstream of *UGT8* may be negatively associated with singing accuracy. This study thus provides promising evidence that singing accuracy may be heritable and possibly associated with the gene *UGT8* on chromosome 4q.

A candidate gene association study by Morley et al. (2012) investigated the relationship between singing participation and allelic variants of the genes *AVPR1A* and *SLC6A4.* An overall association with choir participation was observed at the STin2 (intron 2) polymorphism in the *SLC6A4* gene, with the STin2 9-repeat and 12-repeat alleles being more common in choral singers, and the 10-repeat alleles more common in controls (defined as individuals with no regular participation in any organized musical activity; e.g., choir, dance class, orchestra, or rock band). No significant differences in allele frequencies were observed between the two groups for other *SLC6A4* and *AVPR1A* polymorphisms. Previous studies have reported possible involvement of STin2 in personality traits and reward behavior (Kazantseva et al., 2008; Saiz et al., 2010; Zhong et al., 2009). *SLC6A4* polymorphisms (together with *AVPR1A*) have also been linked to participation in creative dance (Bachner-Melman et al., 2005). As several studies have observed associations between *AVPR1A* polymorphisms and certain musical traits such as music memory, music perception ability and music listening behavior (Granot et al., 2007; Ukkola-Vuoti et al., 2011; Ukkola et al., 2009), the non-significant *AVPR1A* association in this study led the authors to speculate that the observed STin2 effect may be related to social behavioral characteristics (i.e., a “predisposed to group activity” phenotype) rather than being music-related per se.

Rhythm Production

So far, no genetic studies have focused specifically on rhythm production ability. As noted previously in this chapter, a study investigating speech and language disorder in a family pedigree showed that the affected family members were impaired in rhythm perception and production (Alcock et al., 2000), and all of them had a mutated copy of the *FOXP2* gene (Lai et al., 2001)

MUSIC CULTURE

An association between music culture and genes has been demonstrated in several recent studies, even though music culture is typically viewed as an environmental factor that influences musical ability. In one study, traditional songs from 39 African cultures were classified by their music characteristics such as yodeling and tempo (Callaway, 2007). When the music styles of the various African cultures were compared with a database of African genotypes, a correlation between genes and music culture was found, which suggests that cultures that are musically similar also exhibit greater genetic similarity. Importantly, the researchers also found that the correlation between music culture and geographical distance was weaker than the correlation between music culture and genes, supporting this interpretation.

Similarly, in the first comparative phylogenetic study of genetics and folk music, Pamjav, Juhász, Zalán, Németh, and Damdin (2012) established a relationship between folk music styles in 31 Eurasian cultures and genetic distance, with maternal lineages more strongly linked to folk music traditions than paternal lineages. Specifically, they found that significantly similar folk music cultures could predict significant genetic connections in 82% of the cases examined. However, the reverse was not true; close genetic connections were only able to predict similar folk music styles in 28% of the cases. Based on these results, the researchers speculated that a close genetic relation between two populations is indicative of prior physical and biological contact between ancestors of both populations, which may have in turn brought about an interaction and transmission of musical cultures between the two groups and resulted in the similar folk music styles. This work has also identified a common musical style that was prevalent in a large subset of the cultures studied, most of which were closely related genetically. It also leads to the possibility of the existence of a common musical “parent language” from which various folk music traditions branched out and evolved.

Brown et al. (2014) demonstrated a statistically significant correlation between folk song structure and mitochondrial DNA variation in nine indigenous Taiwanese populations, even after controlling for geographical proximity. Notably, although a significant correlation between language and genes in the populations studied was also found, the correlation became insignificant after controlling for geographical proximity. In addition, the correlation between music and language was insignificant, which indicates that the genetic components of music and language may be partially distinct. In particular, an examination of the population structure for genes, music and language for the nine indigenous populations revealed greater similarities in the population structures between music and genes as compared to language and genes. Taken together, these findings suggest the possibility of the coevolution of music and genes and promote the use of music as a novel cultural marker for the study of population migration history, which can serve to complement existing markers such as language.

Collectively, convergent findings from diverse cultural samples as described above give credence to a link between music culture and genes and highlight the importance of genetic influences in shaping the music environment of a human culture and challenges the common perception of music culture purely as an environmental factor.

SUMMARY

Our goal in this chapter has been to describe the molecular genetic bases of various music-related traits, which can now be grouped together and summarized in Figure 1. For the genome-wide transcriptome and positive selection analysis studies (Kanduri, Kuusi, et al., 2015; Kanduri, Raijas, et al., 2015; Liu et al., 2016), the only genes listed are those known to be important in brain function, hearing, the singing network of songbirds, or previously implicated in other music studies.

INSERT FIGURE 1 HERE

To date, some promising and converging findings have begun to emerge from the molecular genetic studies of musical traits. Most notably, the locus 4q22 has been consistently implicated in music-related traits, including music perception ability and music composing. The implication of neighboring loci 4q23 and 4q26 in vocal pitch-matching provide further support of the involvement of this chromosomal region in influencing music-related traits. In addition, the locus 4q22.1 harbors the gene *SNCA*, which has emerged in recent transcriptome studies as a potential candidate gene for music listening and music performance in musically experienced individuals. Given the role of *SNCA* in dopamine-related functions and music's association with dopamine release, as well as *SNCA*'s implication in song perception, learning and production in songbirds, it appears that *SNCA* is a strong contender for influencing music behavior. Moreover, the putative links between *SNCA* and other songbird-related genes (e.g., *GRIN2B*, *FOXP1*, *VLDLR*, *RGS9*, *FOS*) and various music traits suggest the possibility of cross-species evolutionary conservation for auditory perception and vocal production.

Apart from *SNCA*, *FAM49B* at 8q24.21 was another gene noted to be upregulated in musically experienced participants after classical music listening. This finding is in line with past research evidence showing that the locus 8q24 and nearby locus 8q21 were linked to music perception and AP.

The gene polymorphisms of *AVPR1A* on chromosome 12q has also been consistently implicated in music listening, music perception ability, and music memory. On the other hand, the gene *SLC6A4* has been associated with music memory and choir participation. The role of *AVPR1A* in social cognition and behavior has been well-investigated, as has the possible interaction between *AVPR1A* and *SLC6A4* in communicative behavior. The associations of these two genes with various music functions raises the intriguing possibility of an overlap in the neurobiological basis of music functions and social behavior, which appears to be consistent with the evolutionary adaptive role of music in promoting social bonding some researchers have proposed (e.g., Huron, 2001; Tarr, Launay, & Dunbar, 2014).

In conclusion, given the pervasive influence of genetic factors on a vast array of human traits (Polderman et al., 2015), it is not surprising to observe a growing body of genetic evidence for music ability and music-related traits. Future research would benefit from a more precise delineation of music phenotypes, so as to facilitate the identification of specific genetic factors underlying each music phenotype. As the molecular genetic basis of musical traits become increasingly elucidated, it is likely that this will bring new insights into the biological basis of music. Furthermore, the exciting developments and emerging evidence in music genetics research make the stance of radical environmentalism increasingly implausible. It is understandable that some may feel uncomfortable with the notion of music ability being influenced by genes, given their concern about the ethical implications that potentially arise if genetic makeup is used as a basis to reserve music learning resources for a select few and exclude the less endowed from having the opportunity to learn. It is our strong view however, that both biological determinism and radical environmentalism are problematic, and that a complete account of music ability and the development of musical expertise requires both genetic and environmental factors and their interaction to be understood thoroughly.

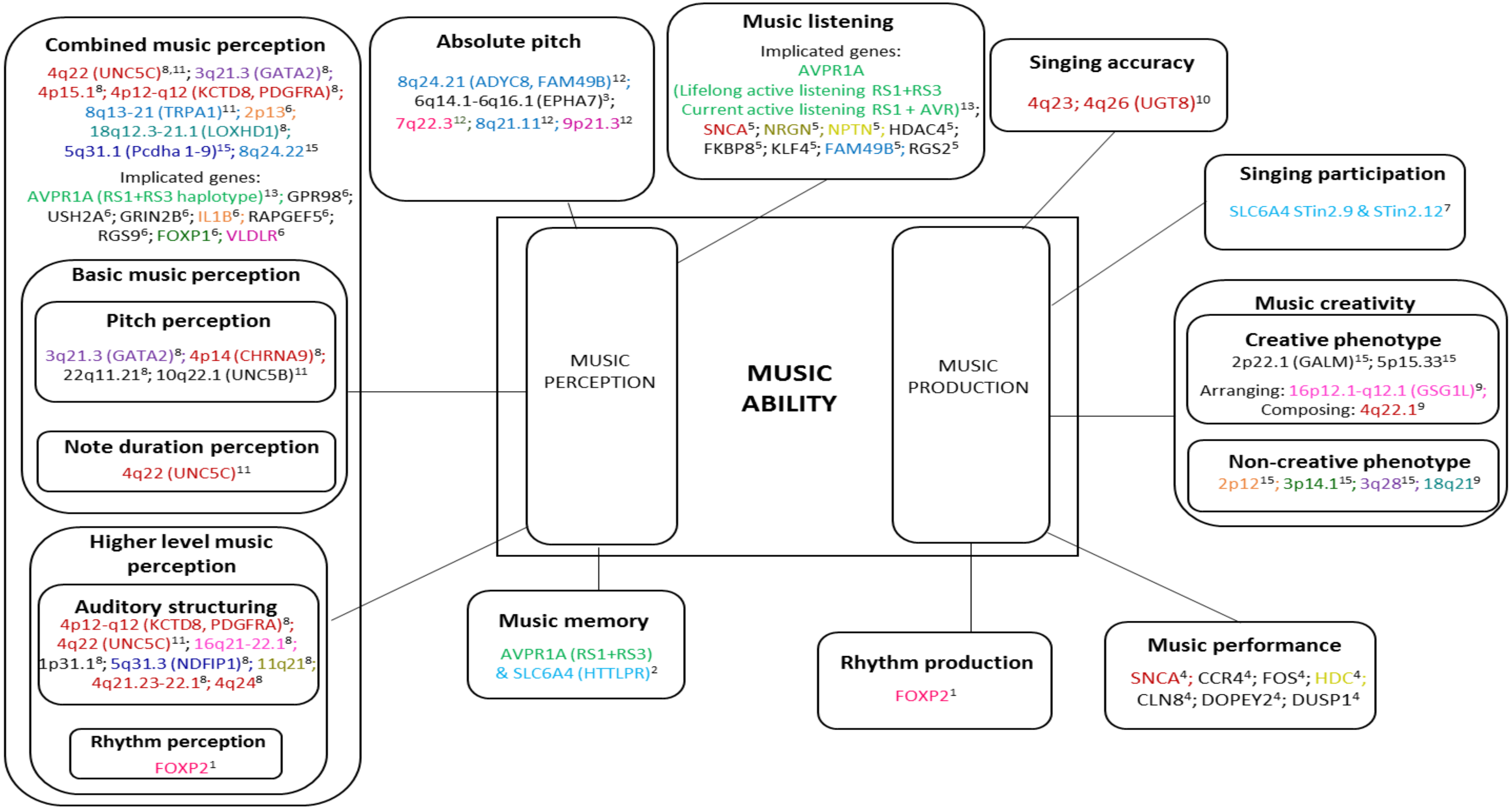

Figure 1. A summary of possible genetic determinants of music ability and music-related traits. Genes or chromosomal loci that are in the vicinity of one another are represented in the same font colors. Potential candidate genes found at an implicated locus are enclosed in parentheses. [1] Alcock et al. (2000); [2] Granot et al. (2007); [3] Gregersen et al. (2013); [4] Kanduri, Kuusi, et al. (2015); [5] Kanduri, Raijas, et al. (2015); [6] Liu et al. (2016); [7] Morley et al. (2012); [8] Oikkonen et al. (2014); [9] Oikkonen et al. (2016); [10] Park et al. (2012); [11] Pulli et al. (2008); [12] Theusch et al. (2009); [13] Ukkola et al. (2009); [14] Ukkola-Vuoti et al. (2011); [15] Ukkola-Vuoti et al. (2013).

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