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ORIGINAL ARTICLE

Association of the arginine vasopressin receptor 1A (*AVPR1A*) haplotypes with listening to music

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Music is listened in all cultures. We hypothesize that willingness to produce and perceive sound and music is social communication that needs musical aptitude. Here, listening to music was surveyed using a web-based questionnaire and musical aptitude using the auditory structuring ability test (Karma Music test) and Carl Seashores tests for pitch and for time. Three highly polymorphic microsatellite markers (RS3, RS1 and AVR) of the arginine vasopressin receptor 1A (*AVPR1A*) gene, previously associated with social communication and attachment, were genotyped and analyzed in 31 Finnish families (*n*=437 members) using family-based association analysis. A positive association between the *AVPR1A* haplotype (RS1 and AVR) and active current listening to music (permuted *P*=0.0019) was observed. Other *AVPR1A* haplotype (RS3 and AVR) showed association with lifelong active listening to music (permuted *P*=0.0022). In addition to *AVPR1A*, two polymorphisms (5-HTTLPR and variable number of tandem repeat) of human serotonin transporter gene (*SLC6A4*), a candidate gene for many neuropsychiatric disorders and previously associated with emotional processing, were analyzed. No association between listening to music and the polymorphisms of *SLC6A4* were detected. The results suggest that willingness to listen to music is related to neurobiological pathways affecting social affiliation and communication.
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INTRODUCTION

Listening to music has multiple measurable effects on brain structure and function.[1–2] However, molecular mechanisms underlying the effects of music perception and listening to music has been relatively rarely studied. Producing and perceiving sound and music facilitates social communication between individuals. The hormone arginine vasopressin (AVP) and its close homolog oxytocin are well preserved in evolution[3] and have been shown to modulate many social behaviors.[4–5] The arginine vasopressin receptor 1A gene (*AVPR1A*) encodes for a receptor molecule, a neuropeptide that mediates the influences of the AVP hormone in the brain.[6] AVP has an important role in memory and learning.[7] *AVPR1A* has been shown to modulate social cognition and behavior, including attachment, social bonding and altruism in humans and other species.[4] Recently, we have reported the association of *AVPR1A* haplotypes with musical aptitude and with creativity in music; that is, composing and arranging music.[8]

Music is able to evoke a wide spectrum of emotions.[9] Serotonin- and dopaminergic systems have been associated with emotional processing. The role of the *SLC6A4* polymorphism 5–HTTLPR has previously been studied in reward-seeking behaviors,[10] and in neuropsychiatric conditions.[11–12] *SLC6A4* together with *AVPR1A* polymorphisms have been reported to associate with artistic creativity in professional dancers[13] and with short-term musical memory.[14] The human serotonin transporter (*SLC6A4*; *5-HTT*) is expressed in the brain, mainly in the areas involved with emotions in the cortex and limbic systems. *SLC6A4* removes serotonin released into the synaptic cleft and has been shown to affect amygdala activation.[15] The polymorphic region (5-HTTLPR) that modifies the promoter activity of *SLC6A4* and the variable number of tandem repeats (VNTRs) in intron 2 have been studied in many neuropsychiatric disorders.[16–17]

Here, we investigated the role of the aforementioned candidate genes in active and passive listening to music in extended Finnish families tested for musical aptitude.

MATERIALS AND METHODS

Participants

A total of 31 Finnish families with 437 family members (mean age 42 years, range: 8–93 years) participated in the study. Of the families under study, 19 have been described earlier[8,18] and 12 are new (Figure 1). The nationwide recruitment process of the families has been described earlier.[18]

Music tests

All participants were tested for musical aptitude using the Karma Music test (KMT) designed by one of the authors (KK),[19] Seashore test for pitch (SP) and for Seashore test for time (ST).[20] The characteristics of the tests and testing procedure have been described in detail by Pulli *et al.*[18] Shortly, KMT measures

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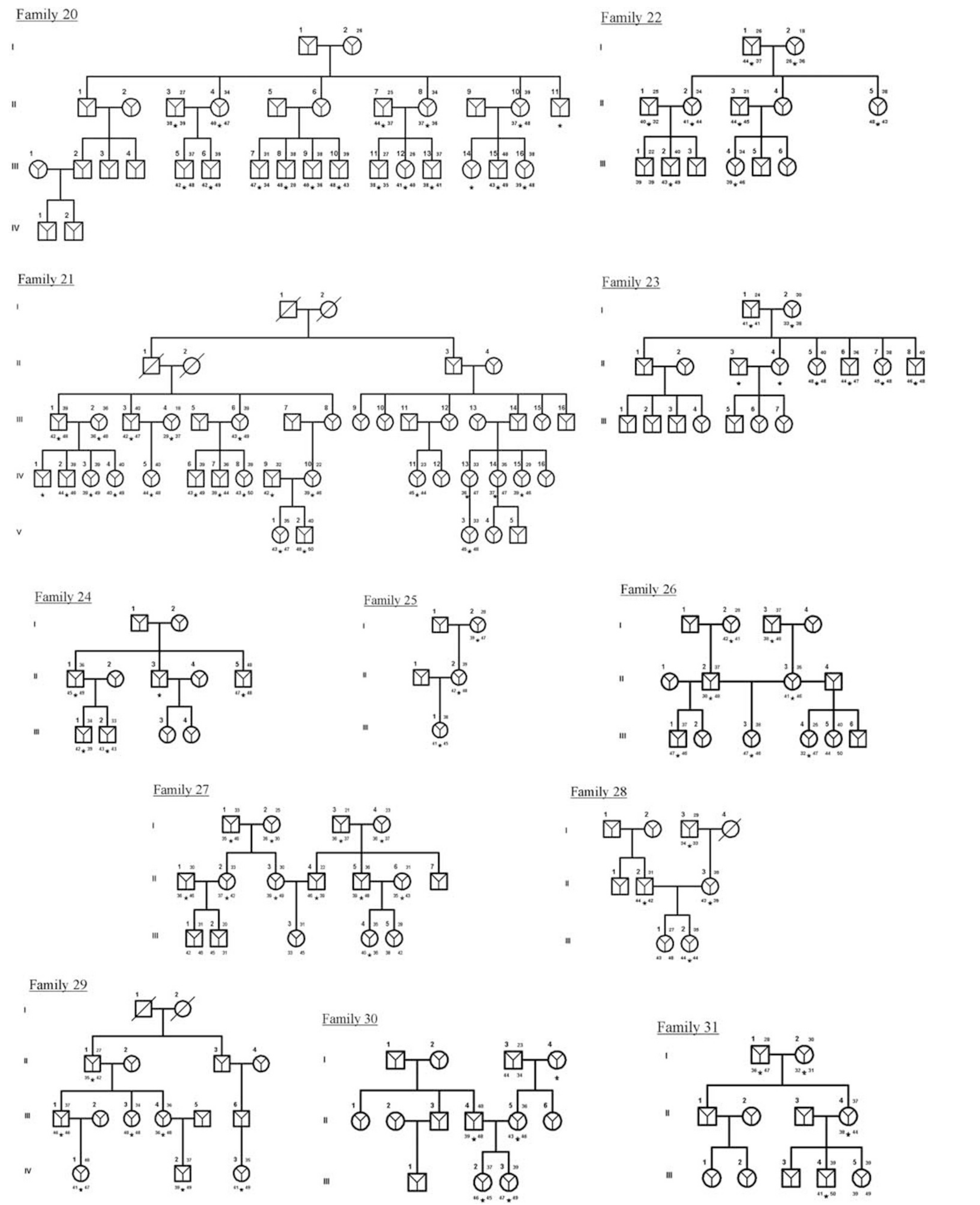

Figure 1 For caption see page 326.

recognition of melodic contour, grouping, relational pitch processing and gestalt principles, the same potentially innate musical cognitive operations reported by Justus and Hutsler.[21] In contrast, the Seashore's tests measure simple sensory capacities, such as the ability to detect small differences in tone pitch or duration that are necessary in music perception. The reliabilities (α-coefficients) of the tests range from 0.78 to 0.91. There is moderate correlation between the three tests ranging from 0.38 between SP and ST, 0.42 between KMT and ST, to 0.61 between KMT and SP ($P<0.001$ for all three), showing that the three tests used in this study measure somewhat different parts of musical aptitude. The heritability estimates of the test scores are: KMT 0.39; SP 0.52, ST 0.10 and combined music score (KMT, SP and ST combined) 0.44.[8]

A total of 368 individuals filled in the web-based questionnaire concerning his/her amounts of music listening and music education. A paper-based questionnaire was also available. Parents answered the questions on behalf of their children who were younger than 12 years of age. To dissect listening habits further, 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 as background music. The average amount (hours) of weekly (1) current active music listening and (2) current passive music listening was asked. Previous music listening was asked in five different age categories: how much a person had been listening in the childhood (<12 years), how much in teenage (12–20 years), in the age of 21–40 years, 41–59 years and beyond 60 years, respectively, up to their present age.

There was an overall increase in music listening from the early decades of the 1900's to present times (manuscript in preparation); that is likely to be caused by an increased availability of music and advanced technology. Therefore, we standardized the listening at each five age categories according to the average amount of music listening in the decades during which each person had been in that specific age class. To minimize the effects of inaccuracy in remembering the amounts of listening, we calculated (3) average lifetime active and (4) average lifetime passive listening per individual, as a simple mean of the standardized weekly amount of listening in different age categories the person had been.

In this article, we report genetic associations between amounts of active and passive current (not affected by recall or the technological level of the society) and lifelong listening to music.

The study was approved by The Ethical Committee of Helsinki University Central Hospital and was conducted in accordance with the Declaration of Helsinki. An informed consent was obtained from all subjects.

Laboratory procedures

EDTA blood samples were available from 416 individuals over 12 years of age. Genomic DNA was extracted from peripheral blood with standard phenol-chloroform procedure. Genotyping of the highly variable microsatellites 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 *AVPR1A* gene was performed (Figure 2).[22] The *SLC6A4* promoter region 5-HTTLPR and the VNTR microsatellite were genotyped as described by Ukkola *et al*.[8] Primer sequences are available on request from the authors.

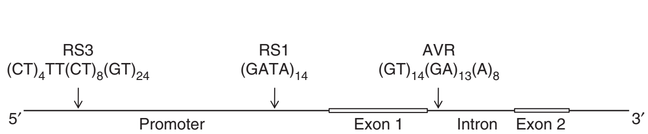

Figure 2 The *AVPR1A* gene with microsatellite markers RS3 and RS1 residing in the promoter region and AVR in intron of the gene. RS3 is located 3625 bp and RS1 553 bp upstream of the transcription start site.

Statistical analyses

A total of 642 individuals were included in the pedigrees and in the statistical genetic analyses. The Mendelian inheritance was assessed using Pedcheck 1.2.1.[23] Hardy–Weinberg equilibrium was tested with PEDSTATS.[24] No departure from Hardy–Weinberg equilibrium was observed for any of the markers. FBAT/HBAT (family-/haplotype-based association test) version 2.0.2c was used to calculate family based association for current weekly active and passive listening, as well as for lifelong listening.[25] Covariates were included through estimation of linear regression models in the PASW statistical program package. 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. The combined music score was computed as the sum of the separate scores of the three individual test results, where KMT music score was first scaled to the same range as the other music scores (ranging from 25 to 50 pts).

The FBAT/HBAT *P*-values presented here were computed using Monte–Carlo samples from the null distribution of no linkage and no association for each haplotype separately, for the global test, and for the minimum observed *P*-value among the haplotypes. The multi-allelic tests circumvent multiple testing problems inherent in highly variable marker haplotypes such as those consisting of RS3, RS1 and AVR, but may be lacking in power. All the results were controlled for multiple testing using permutation on FBAT/HBAT and only permuted *P*-values are reported here. The minimum sample frequency for any haplotype used in the global test (minfreq) was set to 0.01. As HBAT cannot handle more than 80 different haplotypes at a time, the three-marker haplotypes were analyzed using program UNPHASED version 3.1.4.[26] 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. As UNPHASED can use missing data, the power to detect strong effects is generally higher than with FBAT. Genotypes at frequencies lower than 0.05 were excluded. In addition to the default; that is, the additive model of gene function, the dominant and recessive models were also tested. However, no significant deviations from the results by additive tests were observed; thus, these results are not presented here.

RESULTS

Music education, music test scores and listening to music

Mean average active and passive current and lifelong listening to music by music education are shown in Table 1. It was noted that amounts of active, but not passive, listening to music was dependent on music education (correlation $P<0.001$): the more educated individuals tended to listen to music more actively. Current active listening is associated with KMT (K-W; $P<0.005$) and SP (K-W; $P<0.05$) and active listening over lifetime is associated with all music test scores (K-W; KMT $P<0.001$; SP<0.001; ST<0.005). Passive current or over lifetime listening was not associated with music test scores. The association of high music test scores is shown in Figure 3.

Listening to music in pedigrees

Mean current and lifelong active and passive listening to music (h/week) of all individuals in pedigrees with more than four members (*N* from 5 to 35) is shown in Table 2 (12 of the pedigrees shown in Figure 1). Detailed analysis of the pedigrees showed that amounts of mean listening varied in pedigrees (current active from 2.7 to 8.9 and passive from 3.3 to 14.7; lifelong active from 2.6 to 10.1 and passive from 3.3 to 12.7). The variance of the means of lifelong active listening between pedigrees is significant ($P<0.05$). Active listening to music hours was highest in pedigrees 3 and 13 whereas in pedigrees 2 and 18

Figure 1 Pedigrees of the 12 families' (no. 20 to no. 31) participating in the study. Circles illustrating female, squares male and inside triangles music test score (upper score is test score for KMT left, for ST right and for SP). Individuals who had given DNA are marked with an asterisk (*). The generation of the pedigree marked to the left side of each pedigree (from I to V).

Table 1 Mean average active and passive current and lifelong listening to music according to music education.

		Current listening h/week				*Lifelong listening h/week*			
		Active		*Passive*		*Active*		*Passive*	
Music education	*Average KMT scores (max 50)*	N	*Mean*	N	*Mean*	N	*Mean*	N	*Mean*
0	35.2	73	3.6	75	10.0	80	2.7	81	8.2
1	37.9	80	5.6	82	10.3	66	4.3	66	8.6
2	42.3	122	6.7	122	10.2	91	4.4	90	6.5
3	46.8	48	8.3	46	8.0	57	7.9	57	5.8
Total	40.2	323	6.0	325	9.9	294	4.6	294	7.3

Abbreviation: KMT, Karma Music test.
0, no music education; 1, some temporary music education (for example, a maximum of 2 years of music/instrument studies, amateur choir or independent instrumental studies); 2, active amateur (for example, musical/instrumental studies on a regular basis with exams in music/playing or long-term choir activities); 3, professional (music teachers, musicians and connoisseurs).
Active current and lifelong listening to music are correlated to music education ($P<0.001$).

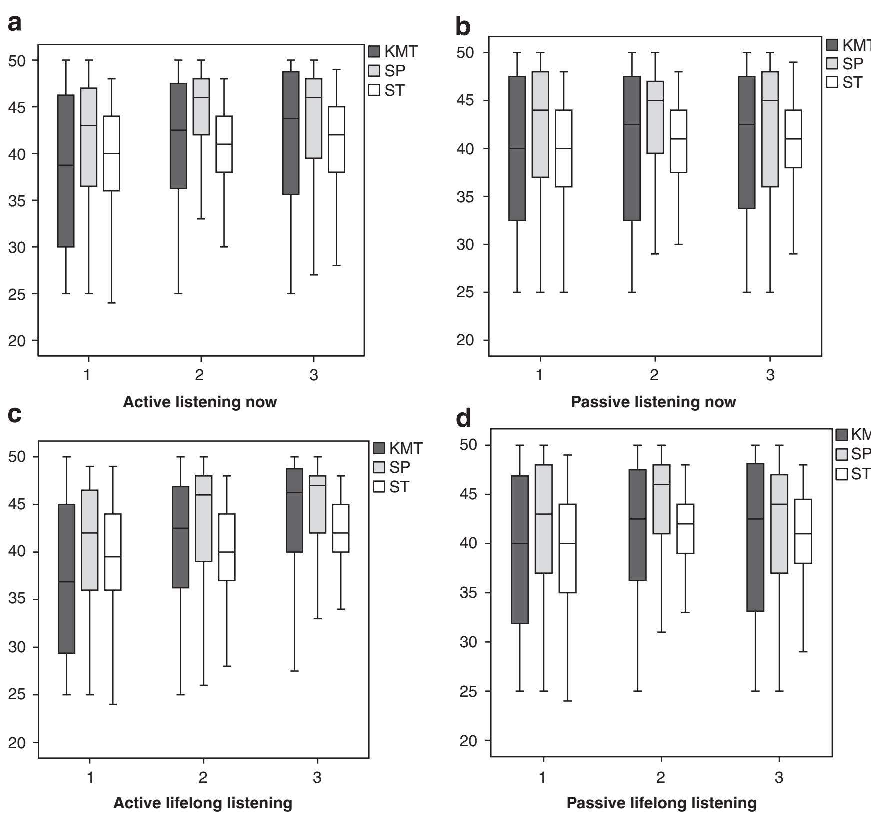

Figure 3 The relationships between current active (**a**) and passive (**b**) and lifelong active (**c**) and passive (**d**) music listening to three music test scores (dark bar KMT, gray bar SP and light bar ST). Y axis: music test scores; *x* axis: categories of listening hours (1 lowest and 3 highest; 33.33% of the data each). Error bars represent the s.e.m. Current active listening (**a**) and active listening over lifetime (**c**) were related to high music test scores whereas passive listening (**b**, **d**) was not.

Table 2 Pedigrees of the study with more than four members and their *N*, current active and passive listening (h/week), lifelong active and passive listening (h/week) and music education (from 0 to 3)

Pedigree no.	*1*	*2*	*3*	*5*	*6*	*7*	*10*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*27*	*30*
N	13	6	6	6	13	7	16	5	23	30	30	16	35	17	11	16	20	10	14	5
Current active listening[a]	3.8	6.6	8.5	6.0	5.4	6.9	5.0	4.6	8.9	6.6	4.4	6.3	4.2	4.9	2.7	8.5	5.0	7.6	4.1	4.7
Current passive listening[a]	3.3	12.5	4.6	11.3	9.5	9.6	8.5	5.4	8.5	9.7	10.6	9.1	9.5	11.3	10.4	14.7	4.7	7.1	6.0	4.8
Lifelong active listening[a]	3.6	7.5	10.1	4.1	4.4	5.9	4.0	4.7	5.5	4.7	3.0	6.2	2.6	3.5	3.0	7.0	4.9	5.7	4.5	2.9
Lifelong passive listening[a]	3.8	11.2	3.3	5.1	9.0	7.8	5.5	4.4	6.1	7.6	7.9	6.5	9.2	10.4	9.3	12.7	4.1	4.9	6.7	6.3
Music education[a]	1.67	1.67	1.63	1.86	0.89	2.00	1.00	2.40	1.10	1.82	1.39	1.70	0.97	0.38	0.93	1.13	2.05	1.42	1.57	1.75

[a]Mean values.

Table 3 Allele and haplotype associations of the *AVPR1A* gene with listening to music (FBAT).

	AVPR1A				
Trait	*RS3*	*RS1*	*AVR*	*Freq./informative fam no.*	P[a]
Active current 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**
	Overall				0.00904
Passive current listening	3	3		0.043/11	0.00886
	5		4	0.019/3	0.00816
Active lifelong listening		**5**		**0.110/30**	**0.00692**
		5	5	0.096/19	0.00730
	6	**4**		**0.017/6**	**0.00221**

Abbreviation: AVPR1A, arginine vasopressin receptor 1A.
The most prominent associations are shown in bold
[a]*P*-values <0.01 are shown, *P*-values permuted.

passive listening was high. In pedigree 20, both mean active and passive listening hours were high (Table 2).

Allele and haplotype analysis

AVPR1A haplotypes consisting of specific alleles of RS1 AVR and RS3 RS1 (Figure 2.) showed strongest association with current active listening (the most prominent haplotype 5 5 with $P=0.0019$; haplotype 2 3 with $P=0.0026$, respectively) (Table 3). Lifelong active music listening showed strongest association with the haplotype 6 4 of RS3 RS1 ($P=0.0022$). In addition, current passive music listening showed association with haplotype RS3 AVR (5 4; $P=0.0082$) and RS3 RS1 (3 3; $P=0.0089$) supporting the idea that both active and passive listening are on the basis of intrinsic attachment behavior sought by listening to music. No additional information was obtained from three marker haplotypes using UNPHASED (data not shown). Adding of music test scores or music education as a covariate did not affect the results.

No significant main effects with *SLC6A4* VNTR or 5-HTTLPR were detected with any of the phenotypes analyzed.

DISCUSSION

Several lines of evidence, including studies on foetuses and infants, family and twin studies, and brain imaging suggest biological background for music.[27–33] Common rules such as use of octave-based scale systems and preference for consonance over dissonance in nearly all types of music can be seen as evidence for innateness.[31] More recently, some evidence for molecular genetic background for music perception has been obtained.[17,32,33] The first genome-wide scan for musical aptitude in Finnish families suggests a multilocus etiology for the trait.[17]

Previously, we have shown that *AVPR1A* haplotypes are associated with musical aptitude, especially with KMT scores, and creativity in music (arranging music).[8] Interestingly, active current listening to music showed an overall association with the same *AVPR1A* promoter region (RS3 RS1) as musical aptitude[8] suggesting a common genetic background. Association of passive listening that was not related to music education or high music test scores suggest that partially same neural circuits are involved in emerging of different aspects, like musical aptitude, listening or arranging of music, in humans. Association with the *AVPR1A* receptor gene that mediates the effects of highly conserved *AVP* further suggests that listening to music is related to the pathways affecting attachment behavior and social communication.[4] In fact, several behavioral features in listening (perceiving) music are closely related to attachment: Lullabies are song to infants to increase their attachment to a parent, and singing or playing music together may add group cohesion.[32]

The dopaminergic and serotonergic systems have been shown to influence cognitive and motor functions in human and animal studies.[8,10,13,34,35] Neurophysiological studies have shown that listening to music has a strong impact on activity in a network of mesolimbic structures involved in reward processing.[34,35] We have previously studied the association between musical aptitude and creativity in music and the polymorphisms of the DRD2 (plus *COMT* and *TPH1* genes), but did not found an association.[8] Here, we did not obtain an association between the polymorphisms of the serotonin transporter gene (5-HTTLPR and VNTR) and any of the traits studied here. Interestingly, Garcia *et al.*[17] reported an association of *SLC6A4* with antisocial personality disorder (APD). The result is in line with the exclusion of associations of *SLC6A4* in this study, suggesting that polymorphisms of *SLC6A4* are rather associated with severe psychiatric diagnosis characterized by antisocial behavior. Further studies in large sample sets are needed to elucidate these questions.

We also tested whether the haplotype associations could merely reflect associations of *AVPR1A* to music test scores, and added them as covariate in the association analysis of music listening, but it did not affect the results. Music education can be seen as an environmental factor in this study as it increases listening to music. Obviously, music education requires active listening to music and is practised by subjects who have been selected to music education programs. In contrast, it can be assumed that passive listening to music does not require high music test scores. However, music education as a covariate did not affect the result, strengthening the genetic effect of *AVPR1A*. Thus, the results suggest that listening to music is independently associated with *AVPR1A*.

In this study, willingness to listen to music and the level of music education varied in pedigrees. Other studies have lately shown familial aggregation of tone deafness,[32] absolute pitch,[33] musical aptitude and creative functions in music (composing, improvising and arranging).[8] In our previous study creative functions in music were shown in some of the pedigrees and missing for others.[8] Interestingly, our pedigrees no. 13 and no. 14 show enrichment of individuals with both creative functions in music and high amounts of active listening to music. Here, we show that active listening to music is related to the level of music education, scores in musical aptitude tests and creative functions in music (correlation $P<0.001$).

Of the participants, 84% answered to the questionnaire demonstrating high motivation to the study. Current listening hours did not deviate significantly from the lifelong listening hours. The accuracy of this information could be dependent on how well a person can recall and assess the true hours, which is in turn dependent on how distant the required age class was from the person's present age.[36] However, there are studies supporting accuracy of retrospective reports, rendering the memory bias explanation less plausible. Twin studies have shown accounts of the individual's current and retrospective reports of family environments equally heritable.[37,38] Furthermore, Kandler *et al.*[38] have shown that genetic influences affected by differences in personality may also influence on the description of recalled rearing environments, and thus on the results how participants remember their music listening habits. The genetically influenced perception process may provoke the professional musicians or individuals particularly interested in music, like the most of the individuals in this study, to remember sharper the details that are related to music.

On the basis of comparative studies similarities between human and animal song have been detected: both contain a message, an intention that reflects innate emotional state (desire for communication, fear or appealing); that is interpreted correctly even among different species.[39–41] Our results further suggest biological contribution to the sound perception (here listening to music). It is obvious that musical aptitude that enables listening to and enjoying music and other traits related to music perception and production represent a complex interaction of predisposing genetic variants and environmental factors encouraging further studies on gene-culture evolution in musical practices.

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