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Absolute Pitch Twin Study and Segregation Analysis

Elizabeth Theusch[1,2] and Jane Gitschier[1,2,3]

[1] *Institute for Human Genetics, University of California, San Francisco, United States of America*
[2] *Biomedical Sciences Graduate Program, University of California, San Francisco, United States of America*
[3] *Departments of Medicine and Pediatrics, University of California, San Francisco, United States of America*

Absolute pitch is a rare pitch-naming ability with unknown etiology. Some scientists maintain that its manifestation depends solely on environmental factors, while others suggest that genetic factors contribute to it. We sought to further investigate the hypothesis that genetic factors support the acquisition of absolute pitch and to better elucidate the inheritance pattern of this trait. To this end, we conducted a twin study and a segregation analysis using data collected from a large population of absolute pitch possessors. The casewise concordance rate of 14 monozygotic twin pairs, 78.6%, was significantly different from that of 31 dizygotic twin pairs, 45.2%, assuming single ascertainment (χ^2 = 5.57, 1 df, p = .018), supporting a role for genetics in the development of absolute pitch. Segregation analysis of 1463 families, assuming single ascertainment, produced a segregation ratio p_D = .089 with SEp_D = 0.006. Unlike an earlier segregation analysis on a small number of absolute pitch probands from musically educated families, our study indicates that absolute pitch is not inherited in a simple Mendelian fashion. Based on these data, absolute pitch is likely genetically heterogeneous, with environmental, epigenetic, and stochastic factors also perhaps contributing to its genesis. These findings are in agreement with the results of our recent linkage analysis.

■ **Keywords:** absolute pitch, perfect pitch, twin study, segregation analysis, genetic heterogeneity

The rare pitch-naming ability absolute pitch (AP), also called perfect pitch, has been a subject of human fascination and scientific study for years (reviewed in Ward, 1999; Zatorre, 2003). Absolute pitch is a perceptual trait, not merely the manifestation of enhanced hearing, and it is associated with anatomical (Keenan et al., 2001; Schlaug et al., 1995) and functional (Klein et al., 1984; Wayman et al., 1992; Zatorre et al., 1998) features in the brain. However, the etiology of this well-defined cognitive ability remains unknown, with current scientific literature suggesting that a variety of environmental and genetic factors may play a role in the development of AP.

Musical training during a critical period of childhood development (Baharloo et al., 1998; Miyazaki, 1988; Sergeant, 1969; Takeuchi & Hulse, 1993) correlates with absolute pitch and likely contributes to its acquisition, but this training alone is insufficient because many people receive early musical training but do not develop AP. In fact, it is difficult to discern whether early musical training predisposes to AP or AP predisposes to early musical training. Other environmental factors suggested to influence whether an individual develops AP include the type of musical training the individual received (Gregersen et al., 2001) and the individual's tone language fluency (Deutsch et al., 2009). Other cultural factors may well influence the development of AP but have yet to be identified.

We and others have hypothesized that the genetic makeup of the individual also contributes to the development of this ability (Bachem, 1940; Baharloo et al., 1998; Gregersen et al., 1999; Profita & Bidder, 1988). Familial aggregation studies have estimated the sibling recurrence-risk ratio (λ_s) for absolute pitch to be between 7.8 and 15.1 after controlling for early musical training (Baharloo et al., 2000; Gregersen et al., 1999). Though this aggregation could be dependent on additional environmental factors that were not considered or controlled for, another

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ADDRESS FOR CORRESPONDENCE: Jane Gitschier, HSE 901, Box 0794, 513 Parnassus Avenue, San Francisco CA 94143 USA. E-mail: jane.gitschier@ucsf.edu

likely explanation is that genetics plays a role in the development of AP. Twin studies could help to determine the relative contributions of genetic and environmental factors to a trait's etiology. To date, three pairs of monozygotic twins concordant for AP and one pair of dizygotic twins discordant for AP have been reported in the literature (Gregersen, 1998), but strong conclusions cannot be drawn from these limited data.

If the etiology of AP indeed has a genetic component, investigating the pattern of inheritance of the trait could lead to a better understanding of how many genetic variants may contribute to AP and in what manner they interact with one another. Since pitch-naming ability appears to be a dichotomous trait rather than a continuous trait, it was proposed that absolute pitch could be influenced by only one or a few major genes (Athos et al., 2007). One group conducted segregation analysis using 19 AP probands with musically educated families and concluded that the inheritance pattern of AP was consistent with autosomal dominant inheritance with reduced penetrance, based on segregation ratios of .24 and .37, assuming single and complete ascertainment, respectively (Profita & Bidder, 1988).

We sought to further test the hypothesis that genetic factors are important for the acquisition of absolute pitch and to better elucidate the inheritance pattern of this trait. To this end, we conducted a twin study and a segregation analysis using data from a large population of absolute pitch possessors.

Subjects and Methods

Because absolute pitch is rare in the general population (Bachem, 1955), we developed a website (http://perfectpitch.ucsf.edu) with an online pitch-naming test and survey to facilitate recruitment of a large number of participants (Athos et al., 2007). The survey included questions about participants' contact information, demographics, musical training, pitch-naming abilities, and family history, including whether the participant was a twin or multiple birth. The most recent version of the survey, launched in February 2008, also asked each participant about his/her ethnicity and number of siblings as well as whether the siblings had absolute pitch, so that a segregation analysis could be performed. Participants were notified at the beginning of the survey that they were giving consent to participate in the survey and note-naming portion of the study by completing the survey and providing their contact information. This study was approved by the Committee on Human Research at the University of California, San Francisco.

Prior to February 2008, 16,504 participants, including some duplicates, took our online survey and/or test. Of these, 4,755 exceeded our most stringent threshold for absolute pitch and were classified as AP-1 (Baharloo et al., 1998). Between February 2008 and March 2010, an additional 7,399 people participated in our test and revised survey, with 2,865 testing as AP-1 (38.7%). There was little sex bias observed; 34% of males and 43% of females tested with AP. It should be noted that the frequency of absolute pitch possession in our study population is far higher than that of the general population and that of the musically trained population due to the ascertainment bias of our website.

Of the individuals who tested AP-1 in our study to date, 31 probands reported a fraternal twin and 14 probands reported an identical twin, and each proband gave us additional information about the pitch-naming abilities of their twin. In some but not all cases these reports of AP were validated if the second twin also entered our study and took our pitch-naming test. We also attempted to corroborate self-reported zygosity through a series of questions for the proband through email; these included report of the number of amniotic sacs and placentas, whether the twins were physically identical, and whether they had been genetically tested for zygosity. Four self-reported monozygotic twin pairs responded that they were confident they were identical based on their physical appearance, and two of these pairs reported being monoamniotic. Monozygosity in one additional twin pair was confirmed in our laboratory by DNA analysis. Five of the twelve same-sex dizygotic twin pairs also responded to our query. Four reported being confident that they were fraternal based on their physical appearance; additionally, two of these four reported being diamniotic and dichorionic, and one of these two pairs reported non-identical blood types. The fifth same-sex, dizygotic pair reported being physically similar, but not the same, and reported two placentas.

Since February 2008, 1,463 of the 2,865 AP-1 probands provided enough accurate information about their siblings to be included in our segregation analysis of absolute pitch families. Participants were disqualified from segregation analysis if they provided inconsistent answers to survey questions, if we had reason to suspect that they were duplicates, or if they did not disclose the numbers of brothers or sisters they had and they did not list their birth order as '1'. Though this probably led to an underestimate of the number of AP probands that were only children in our dataset, it would not affect the segregation ratio. Participants were also excluded from segregation analysis if the birth order they listed was greater than the number of siblings they reported plus one, if they reported more AP siblings than they reported siblings, if they reported an unlikely large number of relatives with AP, or if they answered 'No' or 'Unknown' when asked whether they had family with AP and subsequently reported siblings with AP. In addition, if we could deduce that two or more participants were siblings from the same family, only the survey data from the initial proband was used.

On the rare instances in which we obtained multiple study participants from the same family, they often

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TABLE 1

Absolute Pitch Twin Pairwise and Casewise Concordance Rates

	Monozygotic twins				Dizygotic twins			
Data included	# of pairs	# Conc	Pairwise conc[a]	Casewise conc[a]	# of pairs	# Conc	Pairwise conc[a]	Casewise conc[a]
Confirmed	12	11	84.6%	91.7%	6	5	71.4%	83.3%
Reported	2	0	0%	0%	25	9	22.0%	36.0%
All	**14**	**11**	**64.7%[b]**	**78.6%[c]**	**31**	**14**	**29.2%[b]**	**45.2%[c]**

Note: [a] Calculated under the assumption of single ascertainment (Witte et al., 1999)
[b] χ^2 = 4.56, 1 df, p = .033
[c] χ^2 = 5.57, 1 df, p = .018

reported hearing about the study from a family member, so it is unlikely that two members of the same family were ascertained independently in our study. Thus, we assumed single ascertainment and calculated the segregation ratio and its standard error using the method of Davie (Davie, 1979; Stellingwerff et al., 2006). In sibships with an AP proband, the probability of a sibling of the proband being affected was p_D = (R-J)/(T-J), where R was the total number of AP siblings, T was the total number of siblings, and J was the number of sibships with only one proband.

Results

Accuracy of Sibling Report of AP

Because the ability of AP-1 probands to accurately report whether their siblings have absolute pitch was essential for both our twin study and segregation analysis, we first needed to estimate the accuracy of those reports. To do this, we analyzed families who had participated in our study and in which multiple siblings had taken our pitch-naming test. Out of 154 siblings of AP-1 probands who were reported by the proband to possess absolute pitch, 133 of the siblings indeed tested as AP-1. Of the 21 who did not, 10 scored above the AP-2, AP-3, or AP-4 thresholds (Baharloo et al., 1998), indicating that they possessed pitch-naming abilities that were much better than chance, although they would not be classified as having absolute pitch under our most stringent criterion. In addition, one sibling was only 5 years old and another three were over 50 years old, so the test scores for these four individuals may not have reflected their pitch-naming abilities at a different point in their lifetime (Athos et al., 2007). Thus, a conservatively high estimate for false positive reporting of sibling pitch-naming abilities by probands who are AP-1 was 21/154 or 13.6%. A lower estimate that assumed that all individuals who tested as AP-2, AP-3, or AP-4 had absolute pitch was 7/150, or 4.7%. The false positive rate of 7.7% (1/13) from a previous study (Baharloo et al., 2000) falls between these upper and lower boundaries. This analysis allowed us to make meaningful inferences from sibling reports.

Twin Study

As is evident in Table 1, both the pairwise and casewise concordances of monozygotic twins were greater than the dizygotic twin concordances by a good margin, supporting a role for genetic components in the etiology of absolute pitch. The standard errors of the concordance estimates were also calculated (Witte et al., 1999) and used to determine the significance of the differences between the concordances of monozygotic and dizygotic twins. Though the sample sizes for our twin study were not very large, they were sufficient to achieve statistical significance with greater than 95% confidence. We note also that for the dizygotic twin pairs, the proportion of concordant same-sex twin pairs (5/12; 42%) was quite similar to the proportion of concordant twin pairs of the opposite sex (9/19; 47%), suggesting that reports of zygosity by same-sex dizygotic twin pairs were likely to be accurate.

Segregation Analysis

Our first segregation analysis was conducted on 1,463 families enrolled since February 2008 and revealed a segregation ratio of p_D = .089 with SEp_D = .006 (Table 2). Since one would expect a segregation ratio of 0.25 for autosomal recessive inheritance and 0.5 for autosomal dominant inheritance, it appears that absolute pitch was not inherited in a simple Mendelian pattern in our families. Unfortunately, we did not solicit specific data from most of our probands about the musical training history of their nuclear family members, so we were unable to conduct a more complex segregation analysis incorporating environmental factors, such as musical training history, as covariates.

Because we had detected genetic heterogeneity in our prior linkage analysis (Theusch et al., 2009), we also repeated the segregation analysis in ancestry-specific subpopulations. The largest number of participants reported East Asian ancestry (n = 768), and a substantial number also reported non-Jewish European ancestry (n = 462). Smaller numbers of participants reported Jewish ancestry, African ancestry, Hispanic ancestry, or mixed ancestry. When only families with East Asian ancestry were included (Table 3), p_D =.096 with SEp_D= .009. When only families with non-Jewish, European ancestry were included (Table 4), p_D = .078 with SEp_D =.009.

TABLE 2

AP Family Distribution Based on Survey Data from Participants of all Ethnicities

# AP sibs per family	# families	Total number of siblings per family											
		1	2	3	4	5	6	7	8	9	10	11	12
1	1302	95	755	315	82	32	11	8		1	1		2
2	136		79	43	7	4	2	1					
3	17			14	3								
4	7				4	1	1			1			
5	1					1							
Total	1463	95	834	372	96	38	14	9	0	2	1	0	2

TABLE 3

AP Family Distribution Based on Survey Data from Participants Who Reported East Asian Ancestry

# AP sibs per family	# families	Total number of siblings per family											
		1	2	3	4	5	6	7	8	9	10	11	12
1	691	63	455	151	15	6							1
2	65		46	16		2	1						
3	10			9	1								
4	1									1			
5	1					1							
Total	768	63	501	176	16	9	1	0	0	1	0	0	1

TABLE 4

AP Family Distribution Based on Survey Data from Participants Who Reported Non-Jewish European Ancestry

# AP sibs per family	# families	Total number of siblings per family											
		1	2	3	4	5	6	7	8	9	10	11	12
1	409	17	192	120	46	18	8	6		1	1		
2	44		17	21	3	2	1						
3	5			3	2								
4	4				2	1	1						
5	0												
Total	462	17	209	144	53	21	10	6	0	1	1	0	0

Other AP Relatives Reported

Probands in our study were also asked to report whether they had other relatives with absolute pitch, in addition to siblings. Though these reports were potentially less accurate than the sibling reports, especially for more distant relatives, they still provided some information about how the risk for having absolute pitch varied with the relationship to the proband. Of the entire cohort of 2,865 AP-1 probands who entered the study since February 2008, 422 (14.7%) reported that they had at least one family member with absolute pitch. Specifically, 195 of the 2,189 siblings of probands (8.9%), 161 of the 5,730 parents of probands (2.8%), and 90 of the 11,460 grandparents of probands (0.8%) were reported to have absolute pitch. A variety of more distant relatives, such as uncles, aunts, and cousins, were also reported by the probands to have absolute pitch, but since we did not know how many total relatives each proband had in each of these categories, we could not determine the percentage of relatives reported to have AP in these categories.

Discussion

In this study, we show that there is a genetic component to absolute pitch's etiology, and that the inheritance of absolute pitch is complex. We found that monozygotic twins had a greater concordance for absolute pitch than dizygotic twins and that the segregation ratio in our families was 0.089.

The results of the present study agree with those of our previous linkage study on absolute pitch, which revealed that multiple genetic factors likely play a role in absolute pitch's etiology (Theusch et al., 2009). In that study, we found significant evidence that a genetic marker on chromosome 8q24.21 was linked to absolute pitch in AP families of European ancestry. In addition, we found evidence for a significant excess of linkage peaks in that collection of families, indicating that AP is genetically heterogeneous.

Though we did find considerable differences in twin concordances between monozygotic and dizygotic twins, we predict that increases in sample size would increase the significance of the results. Interestingly, a larger twin study on another pitch perception ability, musical pitch perception tested with a distorted tunes test, indicated the involvement of genetics in the acquisition of that ability, with a monozygotic twin probandwise concordance of 75% and a dizygotic twin probandwise concordance of 57% (Drayna et al., 2001). Thus, genetic factors likely play a role in a variety of aspects of musical sound processing.

It is also important to note that the concordances of monozygotic twins, although quite high, were less than 100% in our study, which indicated that absolute pitch is not solely a genetic trait. Possible explanations for this include differences in environment between twins, the influence of stochastic factors on penetrance of the trait, or epigenetic differences between twins (Fraga et al., 2005). However, differences in musical training between twins could account for the discordant cases. For example, in one of our discordant monozygotic twin pairs, the co-twin reported not to have AP had no musical training, while the co-twin with AP did. Similarly, in a second discordant monozygotic twin pair, the co-twin with AP had musical training on the guitar, while the co-twin reported not to have AP received training on the drums but no tonal instrument.

Though they were quite similar to the overall segregation ratio estimate, the segregation ratio in families of East Asian ancestry was slightly higher than the ratio in families of European ancestry, which may indicate that AP-predisposing genetic and environmental factors may be operating somewhat differently in those two populations. Our previous linkage analysis suggested that the major genetic contributions to AP in these two populations are different (Theusch et al., 2009).

The segregation ratio estimates from our study were all substantially lower than those reported by Profita and Bidder (1988), probably due to differences in sample size and ascertainment criteria. While our study included 1,463 families, they studied only 19 families. We included all AP-1 probands, except those who gave inconsistent or incomplete survey data, who entered our study during a specific time frame. The families from our study resided in many parts of the U.S. and the world, and the musical background of non-proband family members was unknown. In contrast, Profita and Bidder selected their AP probands from musical communities in large metropolitan areas and chose only probands who had musically educated families. While their approach had the benefit of increasing the likelihood that family members had the necessary environmental influences to develop absolute pitch if they possessed predisposing genetic factors, it may also have enriched for families with multiple absolute pitch possessors. Though correlated, the cause-effect relationship of early musical training and absolute pitch possession is unclear. One could imagine that families with multiple absolute pitch possessors would have a higher degree of musical education than other families, and therefore there could have been ascertainment bias for families with a greater number of AP possessors in the Profita and Bidder study.

Absolute pitch was threefold less prevalent in parents of AP probands and elevenfold less prevalent in grandparents of AP probands as compared to siblings. This finding supported the conclusion from the segregation analysis that absolute pitch was not inherited in a fully penetrant autosomal dominant fashion. Even if parents and grandparents of AP probands were genetically predisposed to AP, their musical training was probably more poorly matched to the probands' than that of the probands' siblings, which could result in reduced penetrance. In addition, a combination of genetic factors may be necessary to develop absolute pitch, resulting in a more complex inheritance pattern. It is also worth noting that AP was reported to be about five-fold more prevalent in dizygotic co-twins than it was in siblings of AP probands (45.2% vs. 8.9%), perhaps because twins have a greater shared environment, both pre- and postnatally, than do other pairs of siblings.

Overall, the twin data, segregation analysis, and reports of AP relatives from our study suggest that absolute pitch is a complex trait with multiple genetic and environmental influences.

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