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Defining the Biological Bases of Individual Differences in Musicality

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During the past few decades, our understanding of human biology has been transformed by advances in molecular methods. It has become routine to apply genetic techniques to studies of biomedical disorders, as well as to related traits that show individual variation in the general population. Genetic research has yielded novel mechanistic insights relevant to understanding both disease and normal function. Researchers recently have extended the reach of genetics and genomics beyond standard biomedical traits and have begun to tackle complex human-specific cognitive abilities, such as speech and language, with some success (Deriziotis & Fisher, 2013). Genetic analysis of aspects of musical aptitude is a field that is still in its infancy (Tan, McPherson, Peretz, Berkovic, & Wilson, 2014). In this chapter, we discuss progress thus far and consider the promise that the postgenomic era holds for shedding light on the biological bases of human musicality, broadly defined here as the capacity to perceive (perceptual abilities), reproduce, or create music (production abilities).

As for language, the enormous variability of musical expressions found around the world bears the hallmarks of culture. However, like language, an emerging consensus suggests that musicality may have deep biological foundations and so warrants examination from a genetic perspective (Peretz, 2006). At the same time, if a trait is largely limited to our own species, this poses special challenges for deciphering the underlying biology (see chapters 7 and 11, this volume). When we investigate these kinds of human capacities, it is important that we move beyond questions of species universals and recognize the value of studying variability (Fisher & Vernes, 2015). In particular, major tools of genetics depend on assessing variability in observable aspects of anatomy, physiology, development, cognition, behavior, and so on (*phenotypes*), and then searching for correlations with variations at the genetic level (*genotypes*) (see the glossary below for definitions of italicized technical terms). Variability in musical aptitude is well documented within human populations and is not limited to exceptional cases of virtuoso musicians or, at the other extreme, people who are unable to appreciate or engage with music despite adequate opportunity (Peretz, 2013). Clear evidence has emerged showing considerable individual variation in music-related skills throughout the general population (Müllensiefen, Gingras, Musil, & Stewart,

2014), variation that is likely to have at least some basis in biology (Ullén, Mosing, Holm, Eriksson, & Madison, 2014). Concomitantly, recent efforts to comprehensively catalog the natural variability in modern human genomes have revealed a surprising degree of variation within populations, affecting virtually every genetic locus in some way (Abecasis et al., 2012; Lappalainen et al., 2013). Thus, human populations can be effectively treated as natural experiments for identifying biologically meaningful links between individual variation at different levels (Fisher & Vernes, 2015), allowing researchers to trace causal connections between particular genes and phenotypes of interest—in this case, key features of musicality. Once relevant genes have been pinpointed, they can be used as entry points into the critical neurobiological pathways and potentially complement other approaches to understanding musicality (see chapter 1, this volume).

This should not be taken to imply that there exists a specific "gene for music." Genes cannot directly specify behavioral or cognitive outcomes. They have highly indirect effects at best, encoding molecules (RNAs and proteins) that influence the ways in which neurons proliferate, migrate, differentiate, and connect with each other during brain development or modulate the plasticity of circuits during learning (e.g., Fisher, 2006). Moreover, musicality is a complex multifaceted phenotype, itself comprising many potentially distinct abilities (Levitin, 2012; Müllensiefen et al., 2014), and an array of different genes may be involved. At this point, the genetic architecture underlying music-related skills is largely unknown. While extremes of musical ability might plausibly involve some rare monogenic effects still to be discovered, it is likely that individual differences in the general population involve variants at multiple interacting genetic loci, the number of which has not yet been determined. In addition, environmental influences should not be neglected. Sociocultural variables, exposure to music, and years of music training are well-known environmental factors that have an impact on aptitude (Hannon & Trainor, 2007; Hargreaves & Zimmerman, 1992; Trainor & Unrau, 2012). Indeed, musicality may constitute an ideal system for studying interactions between genes and environment (Baharloo, Johnston, Service, Gitschier, & Freimer, 1998; Hambrick & Tucker-Drob, 2015; Levitin, 2012; Schellenberg, 2015).

People harbor a diverse range of distinct types of genetic variants, which differ in frequency, size, and functional impact.[1] The technology for characterizing genomic variation has been advancing at an astonishing pace as the time and resources needed for genotyping and sequencing have been dramatically reduced. DNA chips allow hundreds of thousands of known genetic variants to be simultaneously genotyped rapidly and at low cost and can easily be scaled up to studies involving thousands of people. The advent of *next-generation DNA sequencing* means that the entire genome of a person can be determined for a few thousand dollars in a matter of days, and the field continues to move forward (Gilad, Pritchard, & Thornton, 2009; Goldstein et al., 2013). Nonetheless, it is important to stress that success in genetic studies of any human trait of interest depends critically on a solid

strategy for defining and characterizing the phenotype. Thus, advances in human genomics need to be matched by parallel advances in the area of *phenomics*.

In this chapter, we first review the evidence concerning the links between genes or chromosomal regions that have been associated with "extreme" musical phenotypes—that is, phenotypes that are found in only a small percentage of the general population and correspond to congenital impairments in musical ability on the one hand or rare faculties (such as absolute pitch) on the other hand. We then move on to variability within the normal range of musical aptitudes of the general population, considering traits such as relative pitch, music perception skills, and musical production and creativity. Finally, we outline future research directions for the field and propose concrete suggestions for the development of comprehensive operational tools for the analysis of musical phenotypes.

Musicality at the Extremes

Disorders of Music Perception

Genetic investigations of neurodevelopmental disorders such as speech apraxia, specific language impairment, and dyslexia have been crucial for uncovering the molecular bases of human speech and language skills (Graham & Fisher, 2013). Similar approaches can help to reveal the biological underpinnings of musicality (table 10.1; Peretz, Cummings, & Dube, 2007; Stewart, 2008). About 3 percent of the general population have difficulty detecting notes that are out of key in melodies, against a background of normal hearing, language and intelligence, and adequate environmental exposure (Peretz & Hyde, 2003). The condition, often called tone deafness, is now referred to as congenital amusia to distinguish this lifelong disorder from acquired forms of amusia that occur as the result of brain lesion (Hyde, Zatorre, & Peretz, 2011; Peretz et al., 2002). Congenital amusia is not only characterized by a deficit in detecting mistuning in both melodic and acoustical contexts, but also by an inability to recognize familiar tunes without the help of the lyrics and difficulties singing in tune. In both perception and production, rhythm is relatively spared (Hyde & Peretz, 2004). The biological basis of the condition is further supported by the identification of brain abnormalities affecting gray and white matter in the right auditory and inferior frontal cortex (Hyde et al., 2007), as well as reduced connectivity between these two regions (Hyde et al., 2011).

Congenital amusia tends to show clustering within families (familial aggregation). That is, the condition is present at higher rates in relatives of affected people than expected on the basis of prevalence in the general population. In 2007, Peretz and colleagues studied seventy-one members of nine large families with an amusic *proband* and seventy-five members of ten control families, assessing amusia with an online battery that included an anomalous pitch detection task, a control time asynchrony detection task, and a detailed questionnaire (Peretz et al., 2007). The results confirmed that congenital amusia

Table 10.1
Investigating the biological bases of musicality through extreme phenotypes and known genetic syndromes

Focus	Type of study	Main findings	Citations
Congenital amusia	Familial aggregation	In 9 large families ($n = 71$) with an amusic proband, 39 percent of first-degree relatives were affected, while in 10 control families ($n = 75$), prevalence was only 3 percent. Sibling recurrence risk ratio was estimated at about 10.8.	Peretz et al., 2007
Absolute pitch	Familial aggregation	Different studies estimated sibling recurrence risk ratios of approximately 7.5 to 15.1. Prevalence was higher in people with early musical training and also in families of East Asian ethnicity; direction of causation unknown.	Baharloo et al., 1998, 2000; Gregersen et al., 1999
	Twin study	Concordance in identical twins (78.6 percent, 14 pairs) was significantly higher than that seen in nonidentical twins (45.2 percent, 31 pairs).	Theusch & Gitschier, 2011
	Pharmacology	Adult males taking valproate (a drug hypothesized to affect critical periods) learned to identify pitch better than those taking placebos.	Gervain et al., 2013
	Linkage analysis	A study of 45 European and 19 East Asian families with multiple AP cases found suggestive linkage for multiple chromosomal regions, with inconsistent patterns in the two data sets. Strongest linkage for chromosome 8q24 in European families.	Theusch et al., 2009
	Linkage analysis	Investigation of 53 families (49 European, 4 Asian) failed to replicate top linkage peaks from prior AP work. High rates (20.1 percent) of self-reported synesthesia in AP led the authors to run combined linkage of 53 AP families with 36 synesthesia families. Strongest joint linkage on chromosomes 6q14–q16 and 2q22-q24.	Gregersen et al., 2013
Musicality in known genetic syndromes	Phenotyping	It has been suggested that children with William-Beurens syndrome (due to 7q11.23 microdeletion) have increased auditory sensitivity, musical interest, creativity, and expressivity. Other studies argue that these children show a wide range of musicality profiles, and some may even have elevated risk of amusia.	Levitin, 2005; Lense & Dykens, 2013; Lense et al., 2013
	Phenotyping	Rare mutations of the *FOXP2* transcription factor gene cause a severe speech and language disorder. One study of musical ability in a particularly large family with a *FOXP2* disruption suggested that mutation carriers had selective problems with perception and production of rhythms, while pitch-related abilities were normal.	Alcock et al., 2000; Lai et al., 2001

Note: Examples are given of the different types of approaches discussed in this chapter, along with key results from the relevant studies.

involves deficits in processing musical pitch but not musical time and also showed strong evidence of familial aggregation. In amusic families, 39 percent of first-degree relatives were affected, as compared to only 3 percent in control families (Peretz et al., 2007). The sibling *recurrence risk* ratio was estimated as about 10.8, meaning that siblings of someone with congenital amusia have an almost eleven-fold increased risk of being amusic themselves.

Observations of familial aggregation are supportive of genetic involvement, but might also be (partly or wholly) explained by shared family environment. As explained in box 10.1, twin studies can be used to pull apart these effects and obtain a robust estimate of *heritability*. To our knowledge, no formal twin study of congenital amusia has yet been reported, but a broader study has shown strong heritability for pitch perception (Drayna, Manichaikul, de Lange, Snieder, & Spector, 2001), as we discuss later in this chapter. Nonetheless, by collecting families in which multiple relatives show congenital amusia (Peretz et al., 2007), it becomes possible to try mapping the locations of potential suscep-tibility genes. Such work is currently under way and will benefit from the recent advances in genomic technologies.

Other forms of congenital amusia that affect rhythm but not pitch have been discovered (Launay, Grube, & Stewart, 2014; Phillips-Silver et al., 2011). So far, the number of cases that have been described is very small. Little is known about the prevalence of such dis-orders and whether they show familial aggregation. These are potentially interesting areas for future investigation.

Rare Faculties

Absolute pitch (AP), the ability to identify or produce a musical tone (e.g., middle C or concert A) without reference to an external standard (Deutsch, 2013), is an unusual skill found in only a small percentage of people. AP involves at least two separate cognitive skills: memory for pitch, which seems to be widespread among humans (Schellenberg & Trehub, 2003) and nonhuman animals (Weisman, Mewhort, Hoeschele, & Sturdy, 2012), and the ability to attach labels to stimuli (e.g., classifying tones with different spectral characteristics, such as piano or voice, and consequently labeling their pitch class), which appears to be rarer (Deutsch, 2013). In early reports, the prevalence of AP in the gen-eral population was estimated to be 1 in 10,000 (Bachem, 1955), but more recent studies suggest that it may be found in as many as 1 in 1,500 people (Profita & Bidder, 1988). It has been proposed that this is a dichotomous trait, with a clear phenotypic separation between AP possessors and non-AP possessors (Athos et al., 2007). Recent structural neu-roimaging studies have suggested that AP is associated with altered cortical thickness and connectivity in a number of brain regions (Dohn et al., 2015). As a discrete and easily quantifiable cognitive phenotype, AP may be particularly suited for genetic studies (Athos et al., 2007; Gregersen, 1998; but see Vitouch, 2003). However, its relevance to musicality

Box 10.1
Do Genes Contribute?

Even without molecular data, it is possible to investigate contributions of genetic factors to phenotypes of interest. For a qualitatively defined trait, such as the presence or absence of a particular disorder, researchers can ask whether cases tend to cluster within families and assess whether inheritance is consistent with simple single-gene patterns of transmission or more likely to involve multiple factors. Increased incidence of a trait in relatives of a proband is often taken as evidence of genetic involvement, but it could also be due to environmental factors shared by family members. Twin studies allow these types of contributing factors to be teased apart.

In its simplest form, this approach assesses concordance of a phenotype in pairs of identical twins (who have almost identical genomes) and compares it to the concordance seen for pairs of nonidentical twins (who share around 50 percent of their genetic variations, just like nontwin siblings). Elevated concordance in the identical twins provides evidence of genetic involvement. In fact, twin designs typically go further by directly incorporating quantitative trait data and using the twin-twin correlation structure to partition the phenotypic variation into that due to additive genetic factors, common environment (shared by twins), and unique environment (unshared by twins). The proportion of phenotypic variance that is accounted for by genetics gives a formal estimate of heritability. Statistical tools have become more sophisticated over the years, and it is now routine to apply structural equation modeling and maximum-likelihood methods to large twin data sets, asking questions that extend far beyond heritability estimation. What is the contribution of genetic factors at different ages, and is this due to the same or different sets of genes? How much of the covariance between two correlated traits involves common genetic or environmental contributions? Are sex differences likely to play a role? Is there evidence of gene-environment interaction or correlation underlying a trait?

Quantitative methods can also be used in multigenerational families for partitioning the observed phenotypic variance and estimating heritability (variance component models). Quantitative genetic methods depend on certain assumptions (outside the scope of this chapter), some of which have been challenged. More important, the concept of heritability itself is often misunderstood by nonspecialists. Heritability is a useful statistic that describes variance in a given population at a specific time with a particular set of genetic variations and environmental factors. It is not an intrinsic fixed property of a phenotype, and it does not reveal anything about the biology of an individual or of how malleable a trait might be. For example, heritability estimates of certain features (including general intelligence) are well known to increase with age. Changes in environment (such as many of the developments of modern medicine) can radically alter the heritability of a trait, either diminishing or exaggerating the relative contributions of genetic variation.

remains questionable, especially given that most professional musicians do not possess AP (Gregersen, 1998).

Profita and Bidder (1988) were among the first to explore the hypothesis of a genetic basis for the condition in a study of thirty-five people with AP across nineteen families. Subsequent familial aggregation studies reported sibling recurrence risk ratios between 7.5 and 15.1 (Baharloo et al., 1998; Baharloo, Service, Risch, Gitschier, & Freimer, 2000; Gregersen, Kowalsky, Kohn, & Marvin, 1999), consistent with a role for genetic factors. Further evidence of a significant genetic contribution has been found in studies of twins with AP; the concordance of the condition in fourteen pairs of identical twins was 78.6 percent, compared to a concordance of 45.2 percent in thirty-one pairs of nonidentical twins (Theusch & Gitschier, 2011).

Environmental factors are also strongly implicated in AP, albeit in a complex manner. A robust link between AP and early music training has been uncovered (Baharloo et al., 1998; Gregersen et al., 1999), with a significantly higher prevalence of the condition in people who began their musical training at a very young age. Thus, early music training could potentially be a crucial environmental factor contributing to AP. On the other hand, this same pattern of data could be explained by assuming that a genetic predisposition to AP increases the likelihood that a child receives early music training. Hence, the direction of causation is difficult to establish (Baharloo et al., 1998). In any case, it seems likely that early musical training and genetic predisposition contribute together to the development of AP. Another unexplained observation concerns the higher rates of AP for people of East Asian ethnicity (Gregersen et al., 1999). Again, several alternative hypotheses could account for this well-documented effect; certain cultural groups may respond to early signs of AP with more intensive parental efforts at music education, the increased AP prevalence may be a consequence of culture-specific educational systems that are more effective at fostering this ability, or the findings may have a genetic explanation, reflecting ethnic differences in frequencies of susceptibility *alleles* (Gregersen et al., 1999).

A recent intriguing observation comes from studies of valproate, an inhibitor of the histone-deacetylase enzyme, which can act to put a brake on critical-period learning (Morishita & Hensch, 2008). Administration of this enzyme to adult males apparently reopens the critical-period learning of absolute pitch (Gervain et al., 2013). Neuroimaging studies have also been revealing. Relative to non-AP possessors, AP possessors exhibit anatomical differences in the temporal lobe and other areas (Bermudez, Lerch, Evans, & Zatorre, 2009; Loui, Li, Hohmann, & Schlaug, 2011), as well as differences in the cortical processing of pitch information (Loui, Zamm, & Schlaug, 2012; Zatorre, Perry, Beckett, Westbury, & Evans, 1998).

Researchers studying AP have used linkage analyses in families (see box 10.2) to search for chromosomal regions that may harbor genes involved in the condition (Gregersen et al., 2013; Theusch, Basu, & Gitschier, 2009). In a 2009 study, Theusch and colleagues investigated seventy-three families with multiple AP possessors, including forty-five families of

Box 10.2
Tracing Connections between Genotypes and Phenotypes

Familial clustering and twin studies may provide support for genetic involvement in a human trait. How do we pinpoint the critical genes? In the early days of gene mapping, linkage analysis came to the fore. In this approach, researchers treat polymorphic genetic markers like signposts marking different chromosomal regions. They track how such genetic markers are transmitted to different members of a family, asking whether any particular chromosomal interval is linked to inheritance of the trait of interest. Robust statistical methods are used to ensure that an observed co-segregation between a genetic marker and the phenotype is not a chance finding. Linkage analysis is equally applicable to qualitative (i.e., dichotomous or yes/no) and quantitative traits, and can involve a prespecified genetic model or be model free. Data from different families may be combined; if the same genetic factors influence the phenotype (even if the precise mutation differs in each family), this may help localize the gene(s) responsible. Nonetheless, linkage has low resolution, implicating large regions (loci) containing multiple genes, and it is not well suited for detecting genetic effects that account for only a small proportion of phenotypic variance.

Association analysis, a complementary method with different strengths and weaknesses, tests for correlations between particular gene variants and a trait at the population level. It has greater power than linkage to uncover small effect sizes and allows higher resolution mapping. Still, due to linkage disequilibrium, a polymorphism that shows significant association is often not causal, but could be indexing a causal variant (as yet undiscovered) nearby. The first association studies typically focused on testing small numbers of polymorphisms from selected candidate genes, either based on hypotheses about the biology of the trait or targeting regions highlighted by linkage. In recent years, it became quick and inexpensive to carry out systematic genome-wide genotyping capturing much of the polymorphic content of a phenotyped sample, allowing researchers to perform hypothesis-free association screening at high density across the genome. These screens involve an enormous amount of multiple testing (hundreds of thousands of polymorphisms in each individual), so rigorously adjusted thresholds for statistical significance are required to avoid false positives. Together with the fact that most complex traits are likely to involve many genes with very small effect sizes, such studies require sample sizes of thousands of individuals to achieve adequate power. In the postgenomic era, scientists also now make use of CNV data and rare variations emerging from next-generation sequencing studies. Again, the key to success is the use of robust statistics, and replication in independent samples, to discount spurious genotype-phenotype relationships. Ultimately studies of gene function in model systems are needed to demonstrate true causal connections.

European descent and nineteen families with East Asian ancestry. They found suggestive evidence for linkage to several different chromosomal regions, with strongest evidence on *chromosomal band* 8q24.21 in the European families (see figure 10.1A). There was little consistency between the pattern of findings in the European and East Asian data sets; this genetic heterogeneity is interesting in light of the documented population differences in AP prevalence.

In 2013, Gregersen and colleagues studied an independent set of fifty-three AP families (forty-nine European, four Asian) and identified modest evidence of linkage implicating different chromosomal regions from the prior work. More intriguing, this later study also uncovered evidence suggesting phenotypic and genetic overlaps between AP and synesthesia, another rare condition. For people with synesthesia, a stimulus in one sensory modality automatically evokes a perceptual experience in another modality; for instance, particular pitches, keys, or timbres may evoke specific sensations of color. Like AP, synesthesia is thought to involve genetic contributions, with some clues as to chromosomal regions of interest but no definitive genes yet identified (Asher et al., 2009; Bosley & Eagleman, 2015). Gregersen et al. (2013) uncovered unusually high rates (20.1 percent) of self-reported synesthesia in people with AP, which motivated them to do a joint linkage study, combining their set of fifty-three AP families together with thirty-six families from a prior screen of synesthesia (Asher et al., 2009). Joint evidence of linkage was seen on chromosomes 6 and 2, but since the regions implicated are large and contain many genes (see box 10.2), further studies are needed to pinpoint potential causal variants.

A possible drawback of most AP studies published so far is that they rely on the explicit labeling of pitches and therefore are limited to people with musical training. However, methods have been developed for detecting AP without requiring explicit labeling (Plantinga & Trainor, 2008; Ross & Marks, 2009; Ross, Olson, Marks, & Gore, 2004). Thus, musical training may not be necessary for AP (Ross, Olson, & Gore, 2003), underlining the need to test for the presence of this condition in nonmusicians.

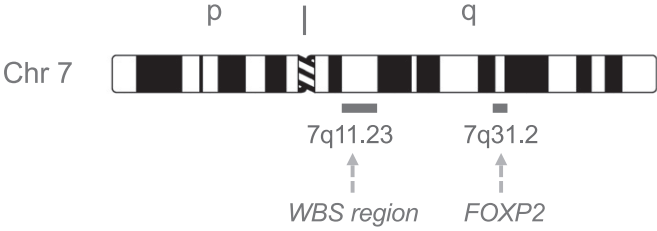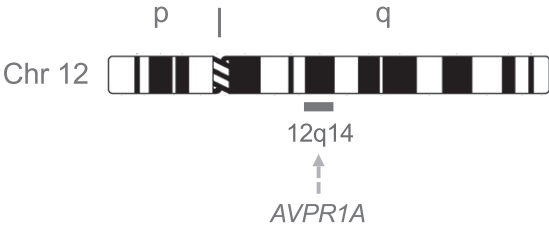## Altered Musicality in Known Genetic Syndromes
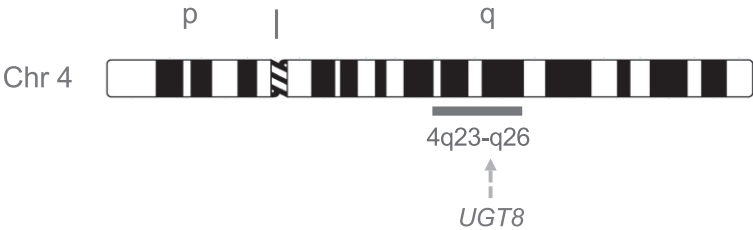
The discussions so far concern identification of rare music-specific conditions, followed by a search for genetic correlates. A complementary approach is to target existing syndromes, where the causative gene or genes are already known, and investigate whether there are any consequences for the musicality of affected people (table 10.1). This is an area that has been little explored but could prove fruitful. Here, we briefly mention two examples from the literature, both of which (by coincidence) involve genes on chromosome 7 (figure 10.1B). Williams-Beuren syndrome (WBS) is a well-characterized microdeletion syndrome with a prevalence of about 1 in 7,500 people, in which as many as twenty-eight neighboring genes in 7q11.23 may be deleted (Martens, Wilson, & Reutens, 2008). People with WBS often show a distinctive cognitive/behavioral profile, which has

Figure 10.1

Connecting genes to musicality: Some selected examples from the literature. Ideograms of chromosomes are shown with the cytogenetic bands of interest indicated. Each chromosome has a short (p) arm and a long (q) arm, separated by a structure called a centromere. When treated with certain stains, chromosomes display consistent banding patterns that are used to denote specific locations with respect to the centromere. (A) Linkage analysis of extreme phenotypes. The first linkage screen of families with AP highlighted a peak on chromosome 8q24.2 (Theusch et al., 2009). Subsequent AP studies have pointed instead to other regions elsewhere in the genome, some of which overlap with linkages to synesthesia (Gregersen et al., 2013). No specific AP-related genes have yet been identified. Linkage analysis has also been used to investigate musical aptitudes using quantitative phenotypes, as detailed in the main text. (B) Studies of musicality in known genetic disorders. Williams-Beuren Syndrome (WBS; Martens et al., 2008) and *FOXP2*-associated speech/language disorder (Fisher & Scharff, 2009), both involving chromosome 7, have been investigated in relation to musicality (Lense & Dykens, 2013; Lense et al., 2013; Levitin, 2005; Levitin et al., 2004) and rhythm (Alcock et al., 2000). (C) Candidate genes. In some cases, particular candidate genes have been targeted based on hypotheses about their biological effects, and polymorphisms have been tested for association with music-related phenotypes. The *AVPR1A* gene is one well-studied example (Bachner-Melman et al., 2005; Morley et al., 2012; Ukkola-Vuoti et al., 2011; Ukkola et al., 2009). However, recent genome-wide screens failed to find significant effects for any prior-studied candidates, including *AVPR1A* (Oikkonen et al., 2014; Park et al., 2012). (D) Copy number variants (CNVs). A recent study searched for CNVs in people with low or high musical aptitude or musical creativity (Ukkola-Vuoti et al., 2013). A number of interesting regions were reported, such as the PCDHα cluster on chromosome 5, found in some individuals with low musical aptitude. Nonetheless, for rare CNVs observed in only a few individuals, it can be difficult to show causality, and so these findings await confirmation in independent samples. (E) Combined approach, using linkage, association, CNV analyses, and sequencing. Park and colleagues (2012) studied pitch production accuracy in a multistage approach. They began with a linkage screen, identifying a broad linkage peak on chromosome 4q23, and followed up with association analyses of the surrounding region, eventually zooming in on the UGT8 gene in 4q26 as a candidate. Further independent evidence to support UGT8 came from identification of a CNV spanning that region as well as variants identified by large-scale sequencing.

been much studied by researchers interested in tracing connections between genes and brain functions. The typical WBS phenotype includes mild to moderate cognitive impairments, disparity between verbal and spatial skills, with receptive language being a relative strength as compared to other abilities, as well as hypersociability, increased empathy, anxiety, and attention deficits (Levitin et al., 2004; Martens et al., 2008; Ng, Lai, Levitin, & Bellugi, 2013). It has been argued that people with WBS show increased auditory sensitivity, heightened emotional responses to music, and relative strengths in musical interest, creativity, and expressivity, in contrast with other neurodevelopmental disorders (Levitin, 2005). Close examinations of particular music perception, production, and learning skills associated with WBS have revealed a more complex story, however, with considerable phenotypic variability from one affected person to another (Lense & Dykens, 2013). These issues are beyond the scope of this chapter but have been discussed in detail recently by Lense, Shivers, and Dykens (2013) and colleagues, who found that the incidence of amusia in WBS is probably higher than that seen in the general population and that the neural correlates of amusia appear to be similar in people with WBS and typically developing individuals (Lense, Dankner, Pryweller, Thornton-Wells, & Dykens, 2014).

Elsewhere on chromosome 7 lies *FOXP2*, a regulatory gene that modulates the expression of other genes (Fisher & Scharff, 2009; see figure 10.1B). Rare mutations that disrupt

A — LINKAGE
Chr 8 — p q — 8q24.2

B — KNOWN SYNDROMES
Chr 7 — p q — 7q11.23 (WBS region) — 7q31.2 (FOXP2)

C — CANDIDATE GENES
Chr 12 — p q — 12q14 (AVPR1A)

D — CNV SEARCHES
Chr 5 — p q — 5q31.1 (PCDHα)

E — COMBINED APPROACH
Chr 4 — p q — 4q23-q26 (UGT8)

FOXP2 cause a severe speech and language disorder. Affected people have problems coordinating sequences of orofacial movements during speech (known as developmental verbal dyspraxia or childhood apraxia of speech), as well as spoken and written impairments in many aspects of expressive and receptive language. A number of different *FOXP2* mutations have been identified thus far (Fisher & Scharff, 2009). One of these has been particularly intensively studied, since it was found in fifteen affected relatives of a large multigenerational pedigree, known as the KE family (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). A study of musical ability in affected members of this family reported reduced performance in tasks involving perception and production of vocal and manual rhythms, while pitch-related abilities appeared to be preserved (Alcock, Passingham, Watkins, & Vargha-Khadem, 2000). These findings are interesting in light of functional evidence implicating *FOXP2* in sensorimotor integration and motor skill learning (Fisher & Scharff, 2009). Further studies of rhythmic abilities in the KE family and other independent cases of *FOXP2* disruption are needed to shed more light on this area.

Genetic Contributions to Individual Differences in the General Population

We now turn our attention to the normal spectrum of musical abilities and survey findings linking individual phenotypic differences to genetic variation (summarized in table 10.2).

Given that pitch perception is a central component of musicality, and perhaps one of the most amenable for large-scale testing, it is not surprising that this facet has been examined more thoroughly than others. In one of the earliest twin studies conducted on music perception abilities in the general population, 136 identical and 148 nonidentical twin pairs were administered the Distorted Tunes Test (Kalmus & Fry, 1980) in which they judged whether familiar melodies contained "wrong notes" (Drayna et al., 2001). The scores on this test, considered a proxy for the participants' ability to judge successive pitch intervals, were estimated to have a heritability of 71 to 80 percent, with no significant effect of shared environment. In a recent study of young adult twins from Finland, 69 identical twin pairs and 44 nonidentical twin pairs (as well as 158 individual twins without their co-twin), were given online tests to assess their melody perception abilities (Seesjarvi et al., 2016). For detection of pitch changes in a task comparing two melodies, about 58 percent of the variance appeared to be due to additive genetic effects. When it came to detection of incongruities in key or rhythm in single-melody perception tasks, a larger proportion of the variance could be explained by the environment, with shared environmental effects accounting for 61 percent of the variance in an out-of-key detection task, and nonshared environmental effects explaining 82 percent of the variance in an "off-beat" task (Seesjarvi et al., 2016). As is standard for twin studies, this report did not identify which specific genes or environmental factors might be involved.

Table 10.2
Investigating the biological bases of musical perception and production through individual differences in the general population

Focus	Type of study	Key findings	Citation
Pitch perception	Twin study	Performance on the Distorted Tunes Test in 136 identical and 148 nonidentical twin pairs from general population yielded heritability estimates of approximately 71 to 80 percent.	Drayna et al., 2001
Musical memory	Candidate genes	Targeted study in 82 students reported provisional association of musical memory with an epistatic interaction between common promoter variants of the genes *AVPR1A* and *SLC6A4*.	Granot et al., 2007
	Pharmacology	Arginine vasopressin was administered to 25 males, yielding effects on musical memory, mood, and attentiveness without affecting digit span.	Granot et al., 2013
Battery of music perception tasks (Karma Test, Seashore Pitch and Rhythm Subtests)	Genome-wide linkage scan	Phenotypic scores in 15 families ($n = 234$) had heritabilities of 42 percent (Karma), 57 percent (Seashore Pitch), 21 percent (Seashore Rhythm), and 48 percent (composite score). Linkage screening revealed a significant peak on chromosome 4q22 and suggestive evidence at 8q13–21. A linkage region on 18q overlapped with one seen in prior studies of dyslexia.	Pulli et al., 2008
	Candidate genes	19 families ($n = 343$) were genotyped for polymorphisms of *AVPR1A*, *SLC6A4*, *COMT*, *DRD2*, and *TPH1*. Some haplotypes of *AVPR1A* were associated with aptitude on the music perception tasks. The other candidate genes showed no significant associations after multiple-testing correction.	Ukkola et al., 2009
	Screen for copy number variants	Study of 5 families ($n = 170$) and 172 unrelated subjects. Nine people with low perception scores carried a 5q31 deletion spanning *PCDHα*; deletion frequency did not significantly differ in people with high scores. Duplication of 8q24 (cf. AP) seen in one person with low scores, but absent in low-scoring relatives. Genome-wide CNV burden did not differ between people with high/low scores.	Ukkola-Vuoti et al., 2013
	Genome-wide linkage and association scan	Linkage scan in 76 families ($n = 767$) identified strongest evidence at 4p14–13 and 4p12–q12, other peaks at 16q21–22, 18q12–21, 22q11. Locations of most linkages differed from prior music-related studies. Genome-wide association scan in same data set found top evidence at 3q21 near *GATA2*. Some association seen for *PCDH7* in 4p15. No association for usual candidate genes (e.g., *AVPR1A*).	Oikkonen et al., 2014
Pitch production	Genome-wide linkage scan and targeted association	Seventy-three families ($n = 1008$) completed pitch production task. Linkage screen in 70 families ($n = 862$) found a significant peak on 4q23. Genotyping of single-nucleotide polymorphisms (SNPs) from the region in 53 families ($n = 630$) revealed significant association near *UGT8*. Authors subsequently identified a nonsynonymous SNP in *UGT8*, and a CNV deletion in the region, each showing association.	Park et al., 2012

Note: Key example studies are shown. For investigations of self-reported musical creativity, see main text.

Genetic contributions to AP have been studied more extensively, most likely because it can be treated as a dichotomous trait, but relative pitch (RP) abilities are probably more relevant to everyday music listening (Miyazaki, 2004). Indeed, RP allows a listener to identify a familiar tune by means of its interval structure (or contour) instead of its constituent pitches (or absolute frequencies), and it allows the detection of "wrong notes." Importantly, AP and RP appear to correspond to two different pitch-processing abilities (Ziv & Radin, 2014), and the RP performance of AP possessors is fairly variable (Miyazaki, 1993; Miyazaki & Rakowski, 2002; Renninger, Granot, & Donchin, 2003). A study by Hove, Sutherland, and Krumhansl (2010) shows that as with AP, individuals of East Asian ethnicity tend to display better RP abilities than Caucasian subjects. Interestingly, this East Asian advantage did not extend to a rhythm perception task and was not modulated by tone language experience.

Few studies have examined the genetic correlates of musical memory, and so far these have focused on testing particular candidate genes for association (see box 10.2 and figure 10.1D). The choice of candidate genes has been motivated by prior studies outside the music domain; for example, some studies of musical memory have targeted arginine vasopressin receptor 1a (*AVPR1A*) and serotonin transporter (*SLC6A4*) genes because common *polymorphisms* of those genes had been previously reported to be associated with creative dance performance (Bachner-Melman et al., 2005). A study of musical and phonological memory in eighty-two students found provisional evidence that these skills were associated with a gene × gene *epistatic* interaction between *promoter region* polymorphisms of the two candidate genes (Granot et al., 2007). In a follow-up to this work, intranasal administration of the arginine vasopressin hormone in twenty-five males was reported to affect musical working memory as well as mood and attentiveness levels, without influencing digit span test scores, suggesting a complex interaction between this hormone, musical memory, and affective states (Granot, Uzefovsky, Bogopolsky, & Ebstein, 2013). Arginine vasopressin and its receptor have been broadly implicated in social behaviors in rodents and humans (Insel, 2010).

A series of studies investigated genetic contributions to musical aptitudes (at multiple levels from heritability to linkage mapping and *association analyses*) in an expanding sample of extended Finnish families (table 10.2; Oikkonen et al., 2014; Pulli et al., 2008; Ukkola-Vuoti et al., 2011, 2013; Ukkola, Onkamo, Raijas, Karma, & Jarvela, 2009). In the first of these studies (Pulli et al., 2008), 15 families (234 people) were tested on a battery of music perception tests comprising the Karma Music Test (Karma, 2007), which measures participants' ability to detect structural changes in abstract sound patterns, and Seashore's pitch and rhythm subtests, which are based on pairwise comparisons (see Ukkola et al., 2009). By analyzing the quantitative phenotype data using a variance component model (box 10.1), the authors obtained heritability estimates of 42 percent for the Karma Music Test, 57 percent for Seashore's pitch subtest, and 21 percent for Seashore's rhythm subtest. Linkage mapping using the quantitative traits revealed significant linkage

on chromosome 4q22, as well as suggestive evidence on chromosome 8q13–21 (Pulli et al., 2008). The latter shows some overlap with a region of suggestive linkage identified in one of the AP studies (Theusch et al., 2009), thus implying a potential link between general music perception aptitudes and rare faculties. Interestingly, there was also some evidence of linkage to a region on 18q that had previously been implicated in developmental dyslexia (Fisher et al., 2002). As we have noted in this chapter, linkage regions are typically large and contain many different genes, so findings of overlapping linkages with distinct phenotypes need further investigation to establish whether there is indeed a shared genetic basis.

Later work by the Finnish group (Ukkola et al., 2009) tested for association of selected candidate genes (based on biological hypotheses from previous literature) with musical aptitudes, as measured by the Karma and Seashore tests, in an expanded data set of 19 Finnish families (343 individuals). Participants were also probed about their musical creativity using a questionnaire; the resulting scores were highly heritable and correlated with performance on the music perception tests. The authors reported that certain *haplotypes* of *AVPR1A* (figure 10.1C) were associated with music perception aptitudes, while there was little support for the variants of the other candidate genes that they tested (serotonin transporter *SLC6A4*, catecol-O-methyltranferase *COMT*, dopamine receptor D2 *DRD2*, and tyrosine hydroxylase 1 *TPH1*). In a follow-up study involving *AVPR1A* and *SCL6A4* polymorphisms (Ukkola-Vuoti et al., 2011), the music listening activities of 31 Finnish families (437 members) were surveyed, suggesting associations between *AVPR1A* haplotypes, but not *SCL6A4* haplotypes, and active music listening.

The same research team also performed a preliminary investigation of genome-wide *copy number variations* (CNVs) in 5 extended families and in 172 unrelated participants (Ukkola-Vuoti et al., 2013). They used the quantitative scores on the Karma and Seashore tests to define cases of low musical aptitude in their sample. A deletion at 5q31.1 (figure 10.1D) was found in 54 percent of "low" cases in two of the extended families, although the frequencies in the other members of these families were not reported, so the strength of the genotype-phenotype correlation remains unclear. In the set of unrelated participants, deletion of 5q31.1 was observed in two of twenty-eight "low" cases (7 percent), as compared to zero of forty cases of "high" musical aptitude, but this difference in frequency is not statistically significant. Nonetheless, since the deletion spans the protocadherin alpha (*PCDHα*) gene cluster (figure 10.1D), which encodes cell adhesion proteins that are important for brain development, the observations warrant further investigation in samples with adequate power. One case of low musical aptitude in one of the large families carried a duplication of 8q24.22, overlapping with the top linkage region from an early study of AP (Theusch et al., 2009), but this CNV did not segregate with the phenotype in the family, making the finding difficult to interpret. The authors also performed CNV analyses in relation to self-reports of musical creativity (Ukkola-Vuoti et al., 2013). For example, they highlighted a duplication of 2p22.1 found in 27 percent of "creative" relatives within

two families; this CNV spanned galactose mutarotase (*GALM*), a gene that is linked to serotonin metabolism. There was no evidence that high or low musical aptitude or musical creativity was associated with an overall increase in CNVs or with an excess of large CNVs (Ukkola-Vuoti et al., 2013).

The Finnish group went on to conduct a genome-wide study of 767 individuals from 76 families, phenotyped with the music perception tests already described (Oikkonen et al., 2014). They screened hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome, using these data to test not only for linkage but also association (see box 10.2). The best evidence for linkage was found on chromosome 4, with strongest peaks at 4p14–13 and 4p12–q12. In this study, there were also weaker regions of linkage at other genomic locations on chromosome 4, including one that showed some overlap with the 4q22 interval implicated in the prior linkage screen on a smaller subset of the families (Pulli et al., 2008). Additional regions elsewhere in the genome showed evidence of linkage in the set of 76 families, including 16q21–22.1, 18q12.3–21.1, and 22q11.1–.21, but they did not replicate any findings from prior studies of music-related phenotypes. Moreover, none of the top linkage regions contained SNPs that showed robust evidence of association with the traits. Although linkage and association are different types of tests (box 10.2), it is unusual that there were no genetic markers showing convergent evidence from both methods (Oikkonen et al., 2014). Neighboring the 4p14 linkage peak but outside the region of linkage evidence, the authors identified association with SNPs that were next to protocadherin 7 (*PCDH7*), a gene known to be expressed in the cochlea and the amygdala. The strongest associations in the genome were observed for SNPs in 3q21.3, in the vicinity of the *GATA2* (GATA binding protein 2) gene. This gene encodes a transcription factor that determines the identity of GABAergic neurons in the midbrain and has been implicated in the development of several organs, including cochlear hair cells and the inferior colliculus. Overall, the study suggested interesting connections to known molecular pathways implicated in auditory processing, but did not support the findings from prior targeted studies on candidate genes such as *AVPR1A* (Oikkonen et al., 2014).

Most recently, the Finnish team followed up their genome-wide study of music perception (Oikkonen et al., 2014) by studying self-reports of musical creativity in this same data set (Oikkonen et al., 2016). For each of two music-related traits—arranging and composing—they used the available self-reported data to produce a dichotomous yes/no classification, that is, designating people who reported such creativity as "cases," and then searched for regions of the genome that were linked to this phenotypic status. No statistically significant linkage was found for musical creativity, but suggestive evidence was observed in a number of regions (Oikkonen et al., 2016). Suggestive linkage for arranging (based on 120 cases) was found for 16p12.1-q12.1. This linkage maps on the same chromosome as the 16q21–22.1 linkage from the authors' prior study of musical aptitude (Oikkonen et al., 2014), although the peaks of the signals lie a large distance from each other, so it is not

clear whether shared genes are involved. More intriguing, a suggestive linkage for composing (based on 103 cases) was observed for 4q22.1, a region that has been highlighted in a number of other studies of musical phenotypes. The authors also studied nonmusical creativity, finding linkage to Xp11.23, based on 259 cases. In fact, the strongest findings of linkage were found for a fourth trait: when people with musical experience but no creative activity (i.e., neither composing nor arranging) were designated as cases, this yielded linkage to 18q21 (based on 149 cases; Oikkonen et al., 2016). In assessing biological pathways highlighted by the suggestive findings of their study, the authors found overrepresentation of genes involved in cerebellar long-term depression, a form of synaptic plasticity that has been well studied over the years. Overall, as with the molecular studies of musical perception reported thus far, the available results point to interesting candidate genes and potential pathways, but lacking statistically significant findings or robust associations for individual genes, it is still difficult to draw firm conclusions concerning the underlying biology.

Few large-scale twin studies have focused specifically on music production abilities. One of the first such studies was conducted by Coon and Carey (1989), who analyzed music-related data obtained from an earlier survey containing a battery of personality and interest questionnaires. Heritability estimates were higher for participation in singing activities than for self-reported music abilities, and heritability was higher for males than for females. A later study used self-reported data from 1,685 twin pairs (twelve to twenty-four years old) to estimate the heritability of aptitude and exceptional talent across different domains such as language, mathematics, and sports, as well as music (Vinkhuyzen, van der Sluis, Posthuma, & Boomsma, 2009). Heritability estimates for music aptitudes were again higher for males (66 percent) than for females (30 percent). However, in both studies, no objective assessment of musical abilities was obtained. More recently, a large-scale study on 10,975 Swedish twins found that the heritability of music achievement was substantially higher for males (57 percent) than for females (9 percent, a nonsignificant influence). The heritability estimates for objectively assessed musical aptitude, however, were 38 percent for males and 51 percent for females (Mosing et al., 2015).

Other studies have explored the interaction between genes, the amount of musical practice, and musical achievement. Using the same large set of Swedish twins, Mosing and colleagues found that music practice was substantially heritable (40 to 70 percent) and that associations between music practice and objectively assessed musical aptitude were predominantly genetic (Mosing, Madison, Pedersen, Kuja-Halkola, & Ullen, 2014). Another study on the Swedish twin sample showed that shared genetic influences explain the association between openness, music flow, and music practice (Butkovic, Ullén, & Mosing, 2015). Working with a sample of 850 twin pairs, Hambrick and Tucker-Drob (2015) reported moderate heritability estimates of music practice and music achievement, and found that genetic influences on musical achievement were strongest among

people who engage in music practice, suggesting the presence of a gene-environment interaction.

Research exploring genetic contributions to music production abilities has largely focused on singing abilities, probably the most widespread such behavior in the general population. Morley and colleagues investigated the *AVPR1A* and *SLC6A4* polymorphisms that were previously associated with musical abilities (Granot et al., 2007; Ukkola et al., 2009; but see Oikkonen et al., 2014, for nonreplication) and creative dancing (Bachner-Melman et al., 2005), testing for their association with choir participation in 523 subjects (Morley et al., 2012). Significant association was detected for a *SLC6A4* polymorphism but not for *AVPR1A* haplotypes proposed to be connected with musical skills in other studies.

Park and colleagues (2012) invited 1,008 individuals from 73 Mongolian families to participate in a pitch-production accuracy test. Family-based linkage analyses using over a thousand genetic markers across the genome identified a peak on 4q23 (figure 10.1E), in an interval that shows some overlap with regions of interest in studies of music perception (Oikkonen et al., 2014; Pulli et al., 2008; note, however, that the genomic positions of the peak regions of chromosome 4 linkage in the most recent Finnish study [Oikkonen et al., 2014] were somewhat different from earlier work on smaller samples [Pulli et al., 2008]). The authors went on to investigate the linked region in detail, using data obtained from SNP genotyping in 53 of the families, and testing for association. They were eventually able to zoom in on a SNP near to the gene *UGT8* (figure 10.1E) showing a highly significant association with performance on the production task. Further analyses uncovered a *nonsynonymous* SNP as well as a CNV in this region that provided further support for a relationship between *UGT8* variations and musical phenotypes (Park et al., 2012). UDP glycosyltransferase 8 catalyzes the transfer of galactose to ceramide, a key step in the biosynthesis of galactocerebrosides, which are important components of myelin membranes in the nervous system.

Phenomics of Musicality in the Postgenomic Era

Dramatic advances in molecular technologies, particularly the development of next-generation DNA sequencing, are set to make a major impact on gene mapping studies of families with music-related disorders or exceptional skills. As for other cognitive traits, the road ahead will still be challenging, since it remains difficult to pinpoint etiological gene variants against a genomic background containing many potential candidates, but developments in analyses of gene function will help to resolve this (Deriziotis & Fisher, 2013). Moreover, the advent of high-throughput large-scale genotyping and sequencing now raises the potential to reliably detect complex genetic effects on musical abilities in the general population. Crucially, investigations of other complex human phenotypes indicate that thousands of participants are needed to achieve adequate power for *genome-wide*

association scans (GWAS; see box 10.2). The largest genetic association studies of musical skills reported thus far (e.g., Oikkonen et al., 2014; Park et al., 2012; table 10.2) have involved sample sizes that are small when compared to GWAS studies in other complex genetic traits, and so have been relatively underpowered. Studies with low power may fail to detect effects that are biologically real. Underpowered studies are also more susceptible to false-positive results in which spurious genotype-phenotype correlations are observed (Button et al., 2013). The lack of replication of linkage and association findings in music-related studies thus far may stem in part from this issue of low power, especially given that the underlying genetic architecture (e.g., number of genes involved, effect sizes) is still unknown. Indeed, this is a problem that has broadly affected studies across human genetics as a whole, including investigations of many standard biomedical traits. These difficulties are now being overcome by improved study designs with high power to accommodate small genetic effect sizes or substantial degrees of heterogeneity.

The success of genetic studies of musical ability also depends critically on a robust, objective, and reliable measure of the phonotype. Yet many of the studies discussed so far have used self-reports (e.g., musical creativity studies [Ukkola-Vuoti et al., 2013; Ukkola et al., 2009], twin studies on music production aptitudes [Coon & Carey, 1989; Vinkhuyzen et al., 2009]). Furthermore, as Levitin (2012) pointed out, scores obtained on traditional assessments of musical aptitude, like the Seashore test, are not highly correlated with real-world musical achievement. The great majority of earlier tests were designed for specific music education purposes (Boyle & Radocy, 1987), and consequently they tend to over-look more general musical skills such as the abilities to verbally communicate about music and use music to efficiently modulate emotional states (Müllensiefen et al., 2014; Murphy, 1999).

Thus, there is a need for objective, validated measures that correlate with expressed musicality and can be used to systematically assess large numbers of people. Ideally, a test battery would have the following characteristics:

1. Capture a broad array of musical abilities including the perception, memory, and production of pitch and rhythm

2. Be designed to be administered to individuals with limited or no formal musical training in order to obtain measures that are widely applicable to the general population

3. Have a version appropriate for preschool children to investigate phenotypic differences before formal musical training

4. Cover a wide range of difficulty so that there is power to detect differences at both the low and high ends of ability, which may be most informative

5. Show only a weak or moderate correlation with broader cognitive measures such as general intelligence or working memory

6. Be culture independent, or at least have culture-independent components, thus allowing comparisons between people from different cultures and reducing confounding factors when assessing potential genetic predispositions associated with specific phenotypes

7. Include covariates such as amount of musical training

8. Be designed to be administered robustly online to enable rapid large-scale phenotyping

9. Be of sufficiently short duration that large numbers of people will agree to participate

A test battery that met these criteria could be administered to population cohorts that have already received genome-wide genotyping for studies unrelated to musical abilities. This kind of phenotype-driven approach could potentially be applied across multiple cohorts, and meta-analyses of the resulting GWAS data sets would yield suitably large sample sizes to achieve high power for detecting subtle genotype-phenotype connections. Other potential practical applications include fractionating musical ability by examining which aspects of musical ability correlate specifically with other cognitive traits or genetic characteristics (Levitin, 2012).

While there have been critiques on fundamental issues of method and control in web-delivered experiments (McGraw, Tew, & Williams, 2000; Mehler, 1999), this type of data collection has great potential for music perception and cognition research, especially in domains where versatility and ecological validity are at stake (Honing & Ladinig, 2008; Honing & Reips, 2008). Probing music perceptual skills can now be done reliably due to recent technological advances in presenting audio over the Internet, for example by using file formats like MPEG4 that guarantee optimal sound quality on different computer platforms at different transmission rates. However, when it comes to collecting and uploading individual sound files, there remains a lack of standardization, most notably with respect to timing. Therefore, music production experiments (such as tapping or singing along with a stimulus) are still unreliable. Hence, it is still most realistic to focus on phenotypes related to music perception abilities while also collecting information on other aspects of the phenotype through survey-style questionnaires.

There are several candidate components of musicality suggested in the literature (see chapter 1, this volume). With regard to perceptual abilities, relative pitch (Justus & Hutsler, 2005; Trehub, 2003), tonal encoding of pitch (Peretz & Coltheart, 2003), beat or pulse perception (Fitch, 2013; Honing, 2012), and metrical encoding of rhythm (Fitch, 2013) are a good starting point for a phenomics of musicality. For example, the following specific tests could, in principle, be implemented in an Internet-based survey that could be administered to a broad population in less than thirty minutes:

•   Relative pitch ability (Müllensiefen & Halpern, 2014)
•   Melodic memory (Müllensiefen et al., 2014)

- Beat perception: identifying the tempo of a musical excerpt by comparing two excerpts in different tempi and judging whether they are different, or judging whether an isochronous rhythm is on or off the beat with respect to the underlying music (task based on Iversen & Patel, 2008; Iversen, Patel, & Ohgushi, 2008; cf. Honing, 2013)
- Meter perception: judging whether two excerpts are rhythmically (dis)similar using classes of rhythms in simple and compound meters (classification task based on Hannon & Trehub, 2005; cf. Cao, Lotstein, & Johnson-Laird, 2014).

Two test batteries covering most of these aspects, the Goldsmiths Musical Sophistication Index (Gold-MSI) questionnaire and test battery (Müllensiefen et al., 2014) and the Swedish Musical Discrimination Test (SMDT; Ullén et al., 2014) have been validated on large populations. The Gold-MSI, which can be completed in twenty minutes, includes a melodic memory task based on a comparison paradigm (Bartlett & Dowling, 1980), a beat tracking task (based on Iversen & Patel, 2008), and a self-report questionnaire covering a broad spectrum of musical behaviors. Furthermore, data from the Gold-MSI have been correlated and validated with other test batteries and with personality measures such as the TIPI inventory (Gosling, Rentfrow, & Swann, 2003). The SMDT, which takes approximately fifteen minutes to complete, includes tasks related to melody, pitch, and rhythm.

Of course, for a fuller understanding of genetic contributions to musicality, there are many aspects of phenotypic variation beyond what is proposed above that could prove to be important. Certain of these aspects could potentially be probed in a less objective manner in questionnaires, or some of them might be administered to subsets of the thousands participating in the core thirty-minute test. For example, sensitivity to expressive timing nuances (Honing & Ladinig, 2009) or musical timbre (Law & Zentner, 2012) might be connected with consistent genetic variation. Psychophysical tasks measuring auditory streaming abilities (Huron, 1989) or the sensitivity to acoustical features such as roughness and harmonicity (Cousineau, McDermott, & Peretz, 2012; McDermott, Lehr, & Oxenham, 2010) could also prove informative, although the sound fidelity they require could be difficult to ensure in an online setting. Despite these difficulties with administration, such tasks are relatively culture free and could form the basis for a test of musicality that could be administered across cultures. Musical production abilities such as pitch reproduction accuracy (e.g., Park et al., 2012) and meter tapping accuracy are undoubtedly critical components of the musical phenotype, but can be evaluated more reliably in the laboratory than using Internet-based experiments. Finally, it would be of great benefit to obtain indexes of social and emotional responses to music, as well as musical behavior in the sense of attendance at and participation in musical events. It would be possible to get at least crude estimates of these attributes through online questionnaires (cf. Mas-Herrero, Zatorre, Rodriguez-Fornells, & Marco-Pallares, 2014).

Broader Perspectives

A primary focus of this chapter has concerned the potential biological bases of individual differences in musical abilities. We note that the phenomics of musicality can also be investigated at the level of populations, although such studies typically involve comparing musical cultures and genetic relationships rather than assessing musical aptitudes. For example, one study has described a relationship between genetic distance and similarity in the folk music styles across thirty-one Eurasian nations (Pamjav, Juhasz, Zalan, Nemeth, & Damdin, 2012). A more recent report obtained significant correlations between folk song structure and mitochondrial DNA variation among nine indigenous Taiwanese populations (Brown et al., 2014). The magnitude of these correlations was similar to that of the correlations between linguistic distance (based on lexical cognates) and genetic distance for the same populations. Interestingly, although musical and linguistic distances were both correlated with genetic distance, musical and linguistic distances were not significantly correlated with one another.

Another complementary approach for deciphering biological pathways implicated in diverse human traits involves analysis of levels of expression of different genes. For example, one might screen a tissue sample to determine how many copies of messenger RNA transcripts are made from a gene of interest. With advances in molecular technology, it is now possible to perform simultaneous systematic expression profiling of all the many thousands of different transcripts in a sample—known as the transcriptome (Lappalainen et al., 2013). By comparing transcriptomes from different cell types in the same person from the same cell type in different people or under different conditions, particular genes or sets of genes that are important for a certain biological pathway can be identified. Two recent studies have sought to determine how transcriptomes might be affected when a person listens to music (Kanduri et al., 2015b) or gives a musical performance (Kanduri et al., 2015a). Detailed discussion of these investigations is beyond the scope of this chapter, but it is worth noting that for practical reasons, such analyses are currently limited to studying changes in gene expression levels in peripheral blood rather than assessing them directly in brain tissue. In such studies, any transcriptome changes that are observed in blood necessarily reflect systemic effects (for example on stress levels) rather than specific changes that are occurring in brain circuits underpinning music processing, so their relevance to learning and memory seems unclear. Although it is established that engaging in musical activities has effects on structural and functional aspects of certain neural circuits and that such effects may well be mediated by altered gene expression in the relevant parts of the brain, most of these are localized transcriptomic changes that do not get transmitted to peripheral blood and are unlikely to be captured by screening nonneural tissue. As an analogy, screening only an arm or a hand in an MRI scanner does not provide a readout of potential changes in the connectivity of the brain tissues involved in practicing or playing a musical instrument. With further advances in gene expression profiling, it might eventu-

ally be possible to assess how transcriptomes change within the circuits of a living human brain, a development that could revolutionize the understanding of molecular mechanisms underlying key cognitive traits such as language and music. In the meantime, it is worth being cautious about the reach of transcriptomics for this field.

Crucially, molecular genetic studies of humans should be seen as one part of a broader framework for identifying the underpinnings of musicality. This might include comparative work assessing relevant skills in nonhuman animals (see chapter 7, this volume). Moreover, new possibilities are opened up once key genes have been identified; their evolutionary history can be traced, including searching for signs of Darwinian selection (for a recent example, see Liu et al., 2016), molecular networks can be teased apart in human neurons, and ancestral functions can be studied in animal models. At the same time, the evolutionary history of cultural markers, including music, can be informed by phylogenetic studies comparing human populations and, possibly, nonhuman animals. New technologies offer promising prospects in both respects. First, the fields of molecular and developmental neurobiology provide an ever-growing tool kit of sophisticated methods that can be used to decipher how particular genes of interest contribute to the development and plasticity of neural circuits in model systems and humans themselves. Second, the implementation of online-based testing procedures enables a systematic assessment of musical aptitudes on an unprecedented scale. Together, these developments will likely result in a paradigmatic shift in this research field, ushering in a new era for the exploration of the biological bases of musicality.

Glossary

Allele   Alternative forms of the same gene or genomic position.

Association analysis   Statistical test of whether there are nonrandom correlations between a certain phenotypic trait (either a qualitatively defined affection status or a quantitative measure) and specific allelic variants.

Chromosomal band   Each human chromosome has a short arm (p) and long arm (q), separated by a centromere. Each chromosome arm is divided into regions, or cytogenetic bands, that can be seen using a microscope and special stains. These bands are labeled p1, p2, p3, q1, q2, q3, … counting from the centromere outward. At higher resolutions, subbands can be seen within the bands, also numbered from centromere outwards.

Copy number variation (CNV)   Structural alteration of a chromosome giving an abnormal number of copies of a particular section of DNA due to a region of the genome being deleted or duplicated. Copy number variants may occur in an array of sizes, from hundreds to several million nucleotides.

Epistasis   When a single phenotype involves interactions between two or more genes.

Genome-wide association scans (GWAS)   Systematic hypothesis-free testing of association at hundreds of thousands (perhaps millions) of different genetic markers across the entire genome. Involves a huge amount of multiple testing, requiring appropriate adjustments when evaluating significance of results, in order to avoid false-positive findings.

Genotype   The genetic constitution of an individual. Can refer to the entire complement of genetic material, a specific gene, or a set of genes.

Haplotype   A cluster of several neighboring polymorphisms on a chromosome that tend to be inherited together.

Heritability   The proportion of variability in a characteristic that can be attributed to genetic influences. A statistical description that applies to a specific population, it can vary if the environment changes.

Linkage analysis   Enables mapping of the rough genomic location of a gene implicated in a given trait. This method tracks the inheritance of polymorphic genetic markers as they are transmitted in families, assessing whether they cosegregate with a trait of interest in a way that is unlikely to be due to chance.

Next-generation DNA sequencing   Newly emerged high-throughput technologies that allow DNA sequences to be determined at dramatically lower cost and much more rapidly than the standard approaches that were previously available.

Nonsynonymous   A nucleotide change in a gene that alters the amino acid sequence of the encoded protein. Contrasts with synonymous substitutions that preserve the usual amino acid sequence.

Phenomics   The robust measurement of physical, biochemical, physiological, and behavioral traits of organisms and how they alter due to changes in genes and environment.

Phenotype   The appearance of an individual in terms of a particular characteristic (e.g., physical, biochemical, physiological) resulting from interactions between genotype, environment and random factors.

Polymorphism   A position in the genome that contains variation in the population and therefore has more than one possible allele. At present, the most commonly studied of these are single nucleotide polymorphisms (SNPs) involving a single nucleotide at a specific point in the genome.

Proband   The index case who triggers investigation of a particular family to isolate the potential genetic factors involved in a given trait.

Promoter region   A region at the beginning of each gene that is responsible for its regulation, allowing it to be switched on or off in distinct cell types and developmental stages.

Recurrence risk   The likelihood that a trait will be observed elsewhere in a pedigree, given that at least one family member exhibits the trait. Can be defined for specific types of relationships, such as siblings.

Acknowledgments

Note

1. A primer on genes and genomes is available online at https://mitpress.mit.edu/books/origins-musicality.

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