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# The Genetics of Language: From complex genes to complex communication

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## Abstract and Keywords

This chapter discusses the genetic foundations of the human capacity for language. It reviews the molecular structure of the genome and the complex molecular mechanisms that allow genetic information to influence multiple levels of biology. It goes on to describe the active regulation of genes and their formation of complex genetic pathways that in turn control the cellular environment and function. At each of these levels, examples of genes and genetic variants that may influence the human capacity for language are given. Finally, it discusses the value of using animal models to understand the genetic underpinnings of speech and language. From this chapter will emerge the complexity of the genome in action and the multidisciplinary efforts that are currently made to bridge the gap between genetics and language.

Keywords: genetics of language, animal models, FOXP2, CNTNAP2, language disorder, gene regulation, molecular networks, speech, vocal learning, neurogenetics

# 37.1 Introduction

THIS chapter discusses the genetic foundations of language and speech, a topic of particular interest for anybody aiming to understand the fascinating phenomenon that is human language. Indubitably there is a genetic basis for language as shown by several salient facts including that we are the only living species capable of it, that human children effortlessly acquire the language(s) of their community, and that there are pathologies affecting language with a clear genetic component. However, its actual genetic foundations, the mechanisms through which pieces of DNA ultimately affect

aspects of language and speech, the manner in which DNA interacts with the environment (culture[1] included) to produce linguistic beings and how this all has evolved, turn out to be exceptionally complex, fascinating, and sometimes even counterintuitive.

We report here on an ongoing, massively multidisciplinary research effort to understand language genetics that has been advancing our understanding for more than half a century, but which has been accelerating during the last two decades due to advances in molecular genetics, statistics, evolutionary biology, and the language sciences. As such, this chapter aims to be both an introduction to the conceptual and methodological bases of genetics relevant (p. 866) for language as well as a snapshot of the most recent findings and most promising avenues of research in the next decade, supplemented by numerous references to the primary literature. The main message of our chapter is that the genetic foundations of language are truly complex, but not indecipherable, and that only an interdisciplinary, empirical approach will be successful in providing the full picture.

Language is an extremely complex phenomenon (as clearly shown by the other chapters in this book) and, while we need to have a relatively well-formed concept of language when embarking on studying its genetic foundations, we feel it is beyond our remit to try to give a detailed definition here. Suffices to say that for our purposes it is not useful to use very constraining definitions that identify a so-called FLN (faculty of language in the narrow sense) as opposed to FLB (in a broad sense) and that propose that fundamentally language is characterized by recursion (Hauser, Chomsky, & Fitch, 2002) or Merge (Hauser et al., 2014). Instead we take the view that language is a complex multicomponent system that has both biological and sociocultural components (Dediu et al., 2013). This broader view naturally allows the integration of multiple lines of research from several scientific fields, using a multitude of methods and even model organisms, into a coherent complex story about language. We can, for example, not only inquire about syntactic structures in modern English but also about patterns of cross-linguistic diversity, we can adduce evidence from historical language change and even the fossil record. Importantly for this chapter, we can understand which genes affect language and speech in humans by looking at natural genetic variation in the population and linking this to the normal range of abilities observed for language or conversely search out rare, deleterious mutations that cause severe disorders of speech and language in humans. We can also actively investigate the functional mechanisms associated with these genes in model organisms such as mice, songbirds, bats, or even in isolated cells in a dish.

But what relevance do mice, bats, or birds have for language and speech (and more so, an isolated cell), you might rightfully ask? If we view language as a broad, complex phenomenon with a biological basis that has evolved naturally (just like anything else) then there are likely to be features of language and speech that we share—in one form or another—with other animals. For example, children need to learn their spoken language[2] through what is generally known as the capacity for *vocal learning*; but some songbirds, dolphins, and bats (among others) also show vocal learning (Janik & Slater, 1997; Knornschild, 2014; Petkov & Jarvis, 2012) and it is much more feasible to study the

neurobiology and genetics of this capacity in non-human models (Vernes, 2017). Thus, much of what we understand about the genetic components of human language and speech can in fact come from such non-human models. Moreover, our language and speech certainly rest on the structure and properties of our brains, larynges, lungs, lips, tongues, ears, and so on, complex organs composed of cells that interact in complex ways during development and functioning. Isolated cells or small populations of cells in a dish, together with comparative animal studies offer some of the best ways to understand these individual processes and the genetic mechanisms involved.

However, no matter how fascinating and complicated the story presented in this chapter might seem, no matter how advanced the methods, how large the datasets, and the sample (p. 867) sizes required, no matter how much computer power is needed, we must again acknowledge that we are truly at the beginning of the road toward a full understanding of the genetic bases of language and speech. We tried to focus on those aspects most likely to withstand the passage of time but unavoidably—this is science!—some of what we write here will be expanded upon, modulated, or simply proven wrong by future advances. Likewise, we currently only understand small pieces of this enormous puzzle, so many aspects of language cannot be addressed here. Nevertheless, we think there are some take-home messages and principles that will survive time: first, there is no single language gene (and even the concept does not make much sense), but rather complex networks of many interacting genes underlie the human capacity for language. Second, we must approach this problem from many perspectives and incorporate information from multiple models and approaches, even if it comes from zebra finches, cell lines, dyslexia, autism, neuroimaging, or massive association studies of speech rate in the normal population. Third, no matter how much we will know about the genetic bases of language and speech we must never forget the cultural side of this evolutionary spiral.

With those thoughts in mind, we will now lay out the fundamental architecture of the genome, how this drives neural development, what we can learn from animal models and how all of this informs our understanding of the genetic mechanisms underlying human speech and language.

# 37.2 The genome

That the human specific ability to acquire and use language depends on some genetic factors transmitted across generations is now well established by a myriad of genetic, familial, and heritability studies (Bishop, 2009; Graham, Deriziotis, & Fisher, 2015; Stromswold, 2001). It then follows that the human genome must encode these factors, providing dynamic information directing the development of our bodies and shaping form and function to allow humans to employ speech and language.

To unravel the genetic underpinnings of language and be able to use this to give insight into how human language arose and functions, it is essential to understand the human genome and how its information is encoded and enacted. Our understanding of the genome has rapidly increased over recent years, revealing how genetic factors operate and interact in order to build integrated biological systems that determine complex traits. Although perhaps counterintuitive at first, many of these general features of the genome are relevant for understanding a specialized ability like language. This is because subtle changes in timing, dosage, and location of action for a molecular pathway that may seem on the surface to be general, can have highly specific effects, influencing particular cells, brain circuits, or behaviors.

In discussing the human genome, herein we refer to the DNA and its physical packaging, which constitutes the entire complement of information needed for the development of a human individual. At its most fundamental level, the information in the genome is encoded by DNA which consists of four nucleotides (which can be represented as the letters; A, G, C, and T). Despite there being only four possible letters in DNA it can direct the assembly of all molecules and proteins that make up cells of the body, how those cells assemble into tissues (p. 868) and organs (e.g., the brain) and how those organs function (e.g., the activity of the brain to produce certain behaviors). This staggeringly complex task is made possible because of many levels of control that allow the genome to produce a variety of outcomes at different times during development and in different places in the body. Thus, despite the fact that every cell in the body starts off with the same genome, an almost unimaginable level of diversity can be produced. This is highlighted by the example of a neuron vs. a muscle cell. Both cell types start with the same basic genetic code, however each displays a vastly different reading of that code. In a neuron, the necessary genes are switched on (i.e., the letters are “read”) that drive neuronal morphology, the formation of synapses, and the presence of ion channels facilitating the transmission of electrical signals (among other things). By contrast, a muscle cell will express genes that allow it to form a tubular morphology, receive input signals from nerves, and translate these into mechanical force.

It is important to note that the genome of a cell is not just used once during development to direct cellular identity and then forgotten. For a cell to continue to perform its normal function and to be able to react to environmental influences or behavioral changes, dynamic and continuous access to the genomic information is required. Thus, the genetic code may be essentially read in a particular way in a neuronal cell[3], but this may change frequently throughout the lifetime of that neuron, allowing it to respond to the different signals it receives over time. An example of this is that during learning, we may strengthen or weaken synapses in our brain to change our behavioral response to a stimulus. This “synaptic plasticity” is well characterized at a molecular level and is facilitated by the switching on or off of specific genes and proteins that influence synapse strength (Shen & Cowan, 2010; Sweatt, 2016).

In the remainder of this section, we will detail how this temporal and spatial complexity and control is embedded in the genome and how genomic factors involved in these processes have been shown to influence language-relevant phenotypes. (e.g., the observable property, characteristics, or traits of a system (Churchill, 1974)).

## 37.2.1 Genes and proteins

DNA in the genome can be broadly classified into two categories, “coding” and “non-coding” DNA. Coding DNA refers to the part of the genome that encodes genes and, perhaps surprisingly, this DNA accounts for only a small fraction of the genome (~2%). The vast majority of the genome (~98%) is non-coding DNA—it does not code for genes. Historically this was called “junk” DNA as it was thought to not have a purpose, however this idea has now been roundly dismissed as it has been discovered that much of this DNA has a crucial role in regulating when, where, and how genes are read (Doolittle, 2013; Ecker, 2012; Pennisi, 2012) (as will be discussed in later sections).

In order to read the genomic code of a cell, the relevant portion of DNA (the gene) is copied into another, very similar nucleotide code (known as RNA) in a process known as transcription (Alberts et al., 2014; Lewin, Krebs, Kilpatrick, Goldstein, & Lewin, 2011; (p. 869) Strachan, Read, & Strachan, 2011). This RNA “message” (messenger RNA or mRNA) is then “translated” by the machinery of the cell, resulting in the production of proteins (Chapeville et al., 1962; Crick, 1958). For this reason, genes were traditionally defined as “DNA that encodes the sequence of a protein” (Lewin, 1990). Broader definitions of a “gene” are now regularly used since it was discovered that certain RNA molecules produced by transcription do not undergo translation into protein, but rather act to influence cellular functions in their RNA form (Bartel, 2004; Phizicky & Hopper, 2010; Rinn & Chang, 2012) (see section 37.2.4). Thus, a more up-to-date definition of a gene is: “a union of genomic sequences encoding a coherent set of potentially overlapping functional products” (Gerstein et al., 2007).

Proteins represent the bulk of the functional machinery within cells that allows the genetic code to direct phenotypic outcomes. For this reason, we will predominantly discuss protein coding genes, although the role of some RNA encoding genes will be addressed in section 37.2.4. Proteins can fulfill an array of different functions in a cell. They may contribute to the shape and morphology of the cell (structural proteins), act as catalysts of chemical reactions (enzymes), form molecular connections between cells allowing them to exchange molecules or signals (channels), and much more.

Because the DNA code dictates the protein code and the protein code dictates protein function, changes at the level of DNA sequence can have severe effects on protein function. This is particularly striking when detrimental mutations are present. Even a single letter change in the DNA can result in severe effects on the concomitant protein product, sometimes even resulting in a complete loss of protein function. Depending on how reliant a particular cell is on the activity of that protein, this can have a range of

consequences (from mild to severe) for how the cell functions or even on its survival. This is a major driver of phenotypic diversity in the human population; small changes at the DNA level might result in a change in a protein that affects something benign like eye color, or highly detrimental (or even lethal) like microcephaly (development of an extremely small size brain) (Faheem et al., 2015; F. Liu, Wen, & Kayser, 2013). Genetic variation that alters or destroys protein function has been linked to language ability in humans—the most well-known example of which is the *FOXP2*[4] gene (see section 37.2.3).

## 37.2.2 Chromatin structure controls access to genes

We have talked about the genetic code being read, and in this context it is easy to imagine the DNA as a long string of letters awaiting transcription. However, this could not be further from reality. The "string of letters" in the genome is in fact stored as a heavily folded, highly condensed three-dimensional molecule. One reason this occurs is physical; it allows the enormous human genome (composed of three billion "letters") to be packaged into a microscopic cell (Strick, Allemand, Bensimon, & Croquette, 1998). The three-dimensional structure is also thought to control which parts of the genome are available for transcription (p. 870) at a given time or place, making it an important factor dictating the complexity generated from the genome.

In a cell, DNA is tightly wrapped around small proteins called histones and then groups of DNA and histones are further condensed into clusters called nucleosomes (Luger, Mader, Richmond, Sargent, & Richmond, 1997). Together this highly condensed structure is called chromatin, which is itself wound many times into increasingly compressed structures, ultimately forming a *chromosome*[5] (see Fig. 37.1). DNA in tightly packed chromatin cannot be read, and must be unwound before this process can occur[6] (Boeger et al., 2005). A major mechanism by which chromatin structure is relaxed and DNA is made accessible for reading is by the activity of proteins encoded in the genome (known as *chromatin remodelers*) which interact with histones to either (i) add a chemical tag to the histone and change its shape, or (ii) move/remove histones in localized DNA regions (Cutter & Hayes, 2015; Kouzarides, 2007). Such *histone modifications* and the resulting chromatin remodeling are known as *epigenetic mechanisms*. These changes can be prompted by developmental, intra/extracellular, or environmental cues and do not directly change the DNA code, but affect how and when the code can be read.

Epigenetic mechanisms are important for the activity of brain circuits (Amador-Arjona et al., 2015; Brami-Cherrier et al., 2014) and are likely to influence, and in turn be influenced by language acquisition and use. However, it is important to note that the epigenetic modifications that occur within neurons over the lifetime of an individual are not passed to the next generation. Only the genetic material contained in the gametes (sex cells) of an organism are inherited and thus the vast array of different chromatin landscapes that are found in different cells of the body are not passed to the offspring (Jobling, Hurles, & Tyler-Smith, 2004). However, this does not mean that there is no heritability of epigenetic factors. An important distinction must be made between the

architecture itself (the specific chromatin marks) and the “architects” (the chromatin remodelers). Chromatin remodeling genes are encoded in the genome and as such their activity can be inherited. For example, if there is a variant within a chromatin remodeling gene that makes it less efficient at responding to environmental cues, this will affect how the epigenetic changes occur in the brain of that individual. The offspring of this individual may then inherit the less efficient chromatin remodeler and for this reason may have a similar epigenetic response to environmental cues as their parent did (Mathies et al., 2015).

In any given cell, many chromatin remodelers are expressed simultaneously, working in a coordinated and combinatorial fashion to mold the architecture of the chromatin structure across the genome. The combination of remodelers and resulting chromatin structure are specific to individual cells, making genes that encode chromatin remodeling highly important for the processes that generate complexity from the genome. Mutations in chromatin remodeling genes can cause complex disorders involving impaired language and thus point to genetic factors that influence the normal development of language-related neural (p. 871) circuitry in the brain. Here we will discuss the example of *MECP2*, mutations of which are the major cause of Rett syndrome—a neurological disorder related to ASD (autism spectrum disorder) (Hagberg, Aicardi, Dias, & Ramos, 1983; Zappella, Meloni, Longo, Hayek, & Renieri, 2001) that involves repetitive movements, apraxia, intellectual disability, and communication impairments (Lyst & Bird, 2015; Pohodich & Zoghbi, 2015). The MECP2 protein modifies chromatin structure to influence how genes are expressed, and this regulation is important for neuron function and neuronal connectivity (Na & Monteggia, 2011; Na, Nelson, Kavalali, & Monteggia, 2013). Loss of *Mecp2* in animal models has shown its importance for the development and function of specific brain regions (Armstrong, 2005; Kishi & Macklis, 2004). Mecp2 activity is crucial during postnatal stages in the striatum, a region controlling executive function and motor output (including vocal-motor control) (Zhao, Goffin, Johnson, & Zhou, 2013). These data suggest that the function of *Mecp2* is still required after embryonic development is completed, and for normal functioning of the circuits controlling motor/cognitive tasks and their response to environmental cues. This fits well with human phenotypes, where children with Rett syndrome (and loss of MECP2 function) often develop normally for a period postnatally, before showing severe regression with symptoms affecting motor outputs, cognitive functions, and language (Lyst & Bird, 2015; Pohodich & Zoghbi, 2015).

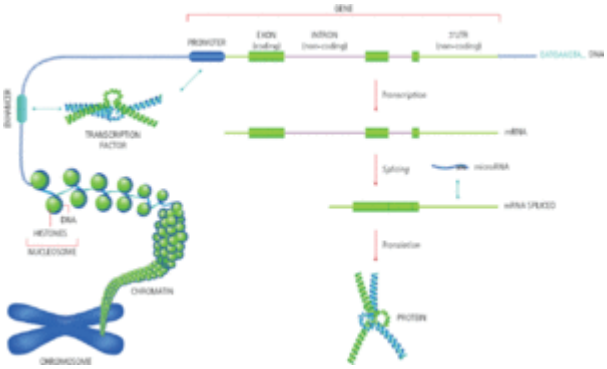
### 37.2.3 Non-coding DNA is a gate-keeper for gene expression

Although chromatin remodeling is crucial, simply unwinding DNA is not enough to ensure the code will be read. Further levels of control then ensure that the right genes are read in the appropriate cell types and time points for normal development and tissue function.

Surrounding each gene in the genome are non-coding DNA sequences that determine how genes are regulated (i.e., when/where they are expressed). Directly before a gene are “promoter” sequences and spaced, often at very large distances from genes, are

"enhancer" sequences (see Fig. 37.1). Both of these regions of DNA interact with proteins in the cell known as transcription factors ("TFs") to facilitate or block the machinery responsible for copying DNA into the RNA message. Thus, by binding to the promoter of a gene, a transcription factor can ensure it is read in that cell type, or prevent its expression.

TFs interact with specific strings of letters in the DNA sequence of promoters and enhancers. These letter strings (motifs) can be as short as six letters and the motif for a given transcription factor may be found in regulatory sequences for thousands of genes (Bulyk, 2003; Hannenhalli, 2008). For this reason, the product of a single TF gene (which can produce many copies of its protein) could bind thousands of regions of the genome simultaneously allowing complex regulation of hundreds or thousands of genes. A single TF often regulates the expression of multiple genes that have similar functions or participate in a shared molecular pathway (Vernes et al., 2011). TFs are often called master regulators—they control the expression of large numbers of genes, some of which will also be TFs and in this way, they can initiate regulatory "cascades" and have substantial effects on cell development and function (Thiel, 2006). For this reason, mutation of a transcription factor can lead to large imbalances in the combinations of proteins expressed by a cell. Such disruptions can severely compromise the morphology, function, or survival of many different cell types, making them strong candidates for causes of cognitive disorders (Thiel, 2006). (p. 872)



Click to view larger

*Fig. 37.1.* Schematic representation of the complexity of the genome. On the left, the structure of genomic DNA is depicted. DNA is wrapped around histones to form nucleosomes and chromatin that is further condensed to form chromosomes. The top part of the figure represents the linear structure of a gene and its regulatory elements (e.g., enhancers and promoters). A gene comprises coding elements (the exons) and non-coding elements (introns and 3'UTR). Red arrows represent the cellular processes involved in the production of proteins from DNA. Transcription factors bind to enhancers and promoters to control transcription of genes into messenger RNA (mRNA). Splicing removes non-coding introns from the mRNA and microRNAs

dynamically bind to 3'UTRs to regulate translation into protein.

(p. 873) Increasing the complexity of this regulation, many TFs rely on interaction with other proteins that regulate transcription (including other TFs) and thus regulation might only occur when the two (or more) required TFs are both expressed at the same time and place. Layer this onto the regulation of the chromatin structure of each gene, and the fact that there are about 20,000 genes in the human genome (Ezkurdia et al., 2014; Ota et al., 2004) and you can start to see the huge diversity and dynamicity that can be generated from this system. Hypothetically, at a single time point, the chromatin surrounding thousands of genes may be unwound, but the cell may only express the TFs needed to drive the expression of a subset of these sites. However, with a change in external signals to the cell, a new transcription factor could be switched on that then drives a whole other subset of these unwound genes or specifically represses some of them blocking an entire genetic pathway.

Several TFs have been implicated in normal speech and language via the identification of mutations in patients with disorders involving speech and/or language deficits. A mutation in the *FOXP2* TF gene was the first case of a monogenic cause of speech/language disorder (Lai et al., 2001). Several unrelated families and individuals have now been identified that have a severe disorder of speech articulation (orofacial dyspraxia) with expressive and receptive language deficits caused by mutation of the *FOXP2* gene (Feuk et al., 2006; Fisher & Scharff, 2009; MacDermot et al., 2005; Rice et al., 2012; Shriberg et al., 2006; Turner et al., 2013). Patient mutations that altered the protein sequence were shown to severely disrupt the function of the FOXP2 protein which normally acts as a transcription factor in the brain (and some other tissues) (Vernes et al., 2006). FOXP2 has been shown to regulate the expression of hundreds of target genes involved in neuronal differentiation, migration, neurite outgrowth, and connectivity (Konopka et al., 2009; Spiteri et al., 2007; Vernes et al., 2011; Vernes et al., 2007), and it is likely that many of these genes are dysregulated in the brains of affected individuals (although we cannot directly measure gene expression in the brains of living people).

Several other TFs have been linked to disorders involving speech and language deficits, and many of these are known to interact with FOXP2, forming a "mini-network." This includes *FOXP1*, a TF gene that is very closely related to *FOXP2* (having similar structure and function) and *TBR1*, a TF involved in brain development and function (Han et al., 2011; Huang et al., 2014). Mutations in both *FOXP1* and *TBR1* cause ASD and people with *FOXP1* mutations also display intellectual disability and speech disorders (Deriziotis et al., 2014; Hamdan et al., 2010; Huang & Hsueh, 2015; O'Roak et al., 2011). It is interesting that with increased patient screening and deeper investigations into the molecular function of mutated genes we are finding that many of the genes mutated in disorders involving language impairment act in overlapping molecular networks. To understand the genetic components of language, it will thus be necessary to understand

these networks and how they relate to one another, a topic we will return to in section 37.3.

### 37.2.4 Who controls the message?

Thus far we have seen that in order to be read, a gene must have the right code, the gene region must be unwound by epigenetic mechanisms at the appropriate time, the right transcription factor (or combination thereof) must be present in the cell, and these must interact with the appropriate motifs in the promoter and/or enhancer of the gene. This complicated (p. 874) cascade of steps all leads to the production of the messenger RNA that is ultimately going to result in production of functional protein. But even at this stage, there is yet another layer of control exerted on the messenger RNA to determine when, where, and how much protein is produced. Two examples of "controlling the message" (also known as post-transcriptional regulation) that we will discuss here are "alternative splicing," and "microRNA-based control of expression."

The mRNA produced from a gene includes not only the coding region of that gene (exons), but also sequences that are not converted into protein. These regions can be at the start or end of the gene sequence (known as the untranslated regions), or within the gene between the blocks of sequence that code for protein (introns). Introns are removed from the messenger RNA before translation into protein in a process called splicing (see Fig. 37.1). To envisage how splicing works, imagine the editing of a movie. From an initial linear recording, only specific clips are retained, and these are stitched together to produce the final film. A similar process turns a long messenger RNA into a shorter, edited molecule that is translated into protein (Berget, Moore, & Sharp, 1977; Chow, Gelinas, Broker, & Roberts, 1977). In the same way that film can be edited to focus on different parts of a story, messenger RNAs undergo "alternative splicing" that removes different parts of the original transcript to result in slightly different proteins (Zheng & Black, 2013). Alternative splicing occurs more frequently in the brain compared to other tissues (Blencowe, 2006; Yeo, Holste, Kreiman, & Burge, 2004), underscoring its importance in generating diversity by increasing the number of different proteins that can be produced by each gene (up to thousands per gene in extreme cases) (Missler, Fernández-Chacon, & Sudhof, 1998).

A family of proteins known as RBFOXs are known to regulate splicing in the brain. All three family members (RBFOX1-3) are strongly expressed in partially overlapping regions of the brain where they regulate splicing of transcripts involved in neuronal development. Mutation of both *RBFOX1* and *RBFOX2* in mice leads to motor and motor learning impairments (Gehman et al., 2012; Underwood, Boutz, Dougherty, Stoilov, & Black, 2005; Zhang et al., 2008). Because they regulate the splicing of many brain expressed messenger RNAs, variations in *RBFOXs* (common variants or rare mutations) have the potential to affect whole networks contributing to brain development and function. Accordingly, these genes have been implicated in neurodevelopmental disorders including ASD, ID (Intellectual Disability), epilepsy, ADHD (Attention Deficit Hyperactivity

Disorder), bipolar disorder, and schizophrenia (Bhalla et al., 2004; Elia et al., 2010; Gehman et al., 2011; Hamshere et al., 2009; Le-Niculescu et al., 2009; J. A. Lee et al., 2016; Martin et al., 2007; Xu et al., 2008). Interestingly, *RBFOX1*, a transcriptional target of FOXP2, underwent evolutionary selection in modern humans (Ayub et al., 2013). This may point to selective pressure on *RBFOX1* related to evolutionary changes in human cognitive functions and possibly language abilities. In a study of people with reading or language disorders, common variation in the *RBFOX2* gene was associated with multiple measures of language and reading (Gialluisi et al., 2014). The variety of phenotypes associated with *RBFOX* genes and their links to FOXP2 reinforce the idea that shared molecular networks underlie language pathways in the brain.

Another mechanism for controlling the message is mediated by a part of messenger RNA known as the 3'UTR (3' Un-Translated Region) which is found at the end of each gene. The 3'UTR exerts fine grained control over how much of the messenger RNA can be translated into protein (Schwerk & Savan, 2015). A well-established function of the 3'UTR (p. 875) is to interact with small molecules called microRNAs (Bartel, 2004; R. C. Lee, Feinbaum, & Ambros, 1993). MicroRNAs are encoded in the genome and are transcribed into RNA, but do not get translated into protein. Instead they are active RNA molecules that interact with the 3'UTR of messenger RNAs (see Fig. 37.1) (Bartel, 2004; Seok, Ham, Jang, & Chi, 2016). This interaction prevents the messenger RNA from being translated into protein by physically blocking this process or degrading the messenger RNA (Bartel, 2004). Genetic variation in either the microRNA or the 3'UTR can interfere with this interaction, affecting gene expression and resulting in disorders (Sun & Shi, 2015; Xu, Karayiorgou, & Gogos, 2010). We recently identified such a variant in a cohort of specific language impairment (SLI)—a disorder characterized by language impairment in the absence of other explanatory factors. The variant was in the 3'UTR of the *ARHGEF39* gene and it interfered with the microRNA regulation of the messenger RNA, resulting in altered expression (Devanna et al., 2017). This variant was found more commonly in affected than unaffected children and was significantly associated with performance on non-word repetition tasks—a common measure for language impairment[7] (Devanna et al., 2017). In future, it is likely that exploring such non-coding variation in the genome will lead to a better understanding of the genetic causes of such disorders and as a result a better understanding of the genetic mechanisms underlying normal language development.

# 37.3 From genes to systems

We have discussed how the genome is non-linear, complex, and dynamic, but how do these concepts translate to the systems level and language? To understand this, we must consider that genes do not act alone, but rather in coordinated molecular networks, and

furthermore understand how these factors influence phenotypes during the development and function of the brain.

### 37.3.1 Genome-wide variation and coordinated molecular networks

The human genome is estimated to code for about 20,000 genes (Ezkurdia et al., 2014; Ota et al., 2004) and each cell expresses a unique combination of thousands of these genes which are dynamically regulated by the mechanisms we have outlined here. The resulting proteins do not act in isolation; rather the thousands of proteins that are simultaneously present in a given cell interact with each other in overlapping molecular networks to produce specific phenotypes relevant for a cell type, time point or response to an external stimulus (Lassek, Weingarten, & Volknandt, 2015).

(p. 876) Recent advances have elevated the study of complex traits from single gene-phenotype connections to the contributions of complex gene networks (Khatri, Sirota, & Butte, 2012). It is now possible to survey across the genome of an individual simultaneously, rather than surveying individual genes and proteins. Genome-wide association studies (GWAS), whole exome sequencing (WES), and whole genome sequencing (WGS) technology sample large numbers of genetic variants spread throughout the DNA of an individual. This makes it possible to consider the phenotype of an individual as the result of the collection of much (or in the case of WGS, all) of the variants in their genome, rather than looking at isolated genes and variants (Burton et al., 2007; Fu et al., 2013; Moorthie, Mattocks, & Wright, 2011; Shendure & Ji, 2008; Visscher, Brown, McCarthy, & Yang, 2012). This presents a formidable challenge given the size of the genome and the estimated three million variants each of us possess in our DNA (Altshuler et al., 2015). However, analysis methods are rapidly advancing, making it possible, under the right experimental conditions and hypothesis, to identify genetic variants associated with phenotypic variation using the normal population as a natural “test-tube” (Narasimhan et al., 2016). These methods have already linked common genetic variants to variation in phenotypic traits like brain volume or activity (Becker et al., 2016; Hibar et al., 2015; Udden, Snijders, Fisher, & Hagoort, 2016), and in the future it is likely that these approaches will also give insight into the wider genetic mechanisms underlying language phenotypes.

At a functional level, ChIP-Sequencing methodology surveys every position in the genome where a transcription factor binds to a promoter/enhancer region (Robertson et al., 2007), making it possible to get a cellular “snapshot” of the hundreds or thousands of genes that are simultaneously being regulated by a protein like FOXP2. Conversely RNA-Sequencing surveys the expression levels of every gene in the genome making it possible to see how mutations or changes in behavior or environmental conditions affect the output of the genome (Hitzemann et al., 2013; Z. Wang, Gerstein, & Snyder, 2009). Coupling these techniques with genome-wide sampling of DNA variation in populations can help to bridge the molecular gap, demonstrating how the genetic variation we

identify in individuals can cause functional changes in gene expression and lead to the resulting phenotypes.

This paradigm shift, from a reductionist to a holistic approach (i.e., considering all the genes expressed in the cell and how they interact) (Fang & Casadevall, 2011) underscores the idea that a single “gene for language” does not exist (Fisher & Marcus, 2006; Graham & Fisher, 2013). Rather, we should appreciate that dynamic, interacting gene networks produce a complex biological system and influence cellular functions that ultimately result in structures (neurological and peripheral) that contribute to language.

## 37.3.2 From genes to phenotypes—migration and neurite outgrowth

Brain development is a complex process that requires many overlapping processes to occur in a precisely timed fashion, directed by the genome. Here we discuss two processes, migration and neurite outgrowth, that are fundamental to brain development, contribute to language-related circuitry, and start to bridge the gap between genes and language phenotypes.

(p. 877) The human cortex is a massive, complex structure crucial for our use and understanding of speech and language (Friederici, 2011; Hagoort, 2013; Hickok & Poeppel, 2007). The cortex can be subdivided into many regions, but always maintains a laminar structure, the majority of which is composed of neurons arranged in specific patterns across six layers (Fernández, Llinares-Benadero, & Borrell, 2016; X. Tan & Shi, 2013). To form this structure, neurons must migrate—often across large distances—to reach their final destination in the appropriate layer of the developing cortex (Fernández et al., 2016; Gao, Sultan, Zhang, & Shi, 2013; Marin, Valiente, Ge, & Tsai, 2010; X. Tan & Shi, 2013). During this process both the final position reached and the timing of the neurons’ arrival are crucial for the normal development of the brain. If either position or timing is altered, the brain may display both structural and functional abnormalities as this mistiming can result in incorrect wiring of the neural circuitry underlying brain function (Sarnat, Philippart, Flores-Sarnat, & Wei, 2015). The migration of neurons during development is influenced by the genes that they and the surrounding cells express: different genes promote or inhibit cellular migration; thus, the specific balance of gene expression determines the neuronal migration pattern (Kwan, Sestan, & Anton, 2012; Luhmann, Fukuda, & Kilb, 2015). In both mouse and animal models, FOXP2 was shown to slow or prevent cellular migration (Clovis, Enard, Marinaro, Huttner, & De Pietri Tonelli, 2012; Devanna, Middelbeek, & Vernes, 2014), suggesting that some of the speech and language phenotypes caused by *FOXP2* mutation could in part be related to subtle neuronal migration defects. Aberrant migration has become a key theme in another language-related disorder, dyslexia. Developmental dyslexia involves deficits in reading and spelling ability in the absence of explanatory factors such as low IQ or reduced opportunity (Paracchini, Scerri, & Monaco, 2007). Large scale searches for the genetic causes of dyslexia have converged on genes involved in migration. *DCDC2, KIAA0319, DYX1C1*, and *ROBO1*—the first and strongest dyslexia candidate genes—all

play a role in directing neuronal migration (Hannula-Jouppi et al., 2005; Meng et al., 2005; Paracchini et al., 2008; Scerri & Schulte-Korne, 2010; Taipale et al., 2003). Aberrant neuronal migration was also identified in the postmortem brains of individuals with dyslexia (Galaburda & Kemper, 1979; Galaburda et al., 1985), supporting this link between migration, dyslexia, and use of written language.

Once neurons have found their appropriate place in the brain they start to “wire up” the neural circuits that underlie behavior. To do this, they must grow long and complex networks of cellular protrusions known as neurites, of which there are two types; axons and dendrites (Chedotal & Richards, 2010). The axon of one neuron extends to connect to the dendrite of another neuron. At this junction a structure known as a synapse is formed which allows information to pass from the axon of one neuron to the dendrite of the next, ultimately resulting in connected neural circuits (Chia, Li, & Shen, 2013). Like migration, the growth of axons and dendrites is influenced by genetic mechanisms (Kolodkin & Tessier-Lavigne, 2011; A. E. West & Greenberg, 2011). At the appropriate time, genes are switched on that drive the growth of these protrusions, but also that control the distance and route the protrusions take, thus controlling which other neurons in the brain they can connect to (Jongbloets & Pasterkamp, 2014). The *FOXP2* gene also has a role to play in this important neurodevelopmental phenotype. Using mouse and human model systems it has been shown that *FOXP2* promotes the outgrowth of neurites and in this way is likely to affect connectivity of neural networks (Devanna et al., 2014; Vernes et al., 2011). The involvement of *FOXP2* in both neuronal migration and neurite outgrowth may contribute to the subtle (p. 878) structural and functional differences that have been observed in speech/language disorder patients carrying mutations in this gene (Liegeois et al., 2003; Watkins, 2011).

### 37.3.3 From genes to phenotypes—synapses and neural circuits

Formation and maintenance of synapses, the physical connections between axons and dendrites, is fundamental to the development and activity of functional neural circuitry (Chia et al., 2013; Krueger, Tuffy, Papadopoulos, & Brose, 2012; Shen & Cowan, 2010). Synaptogenesis—the formation of synapses—begins during late gestational periods and continues at a high rate into adolescence, but at lower rates throughout the lifespan of an individual (Waites, Craig, & Garner, 2005). Once created, synapses can be maintained, strengthened, or pruned depending on the neural signaling that passes through the circuit (Ebert & Greenberg, 2013; Holtmaat & Svoboda, 2009; Shen & Cowan, 2010). Synapses in active circuits will be maintained, but inactive synapses will be pruned. This process (known as synaptic plasticity) is facilitated by the genes and proteins expressed in the cell/synapse and if these genes are mutated, synapses may not be maintained or may not respond appropriately when a neural circuit is activated (Ebert & Greenberg, 2013; Holtmaat & Svoboda, 2009). In addition to regulating cell migration and neurite outgrowth, the *FOXP2* transcription factor also affects synaptic activity and signaling through circuits. In mouse models, loss of *Foxp2* results in altered synaptic plasticity (Groszer et al., 2008) and neuronal firing (French et al., 2012). Given that its function is to regulate the expression of other genes, we can begin to bridge the gap between genes and language phenotypes by understanding how *FOXP2* "target" genes can influence neural circuits.

*FOXP2* was found to regulate the expression of a synaptic gene known as *CNTNAP2* which has been implicated in a range of neurodevelopmental disorders. In particular people with rare mutations in *CNTNAP2* often display language-related disorders including speech apraxia, ASD, language regression, as well as more widespread deficits such as intellectual disability and epilepsy (Rodenas-Cuadrado, Ho, & Vernes, 2014; Rodenas-Cuadrado et al., 2016). Common variation in the *CNTNAP2* gene that can be found spread throughout the population is associated with specific language impairment, ASD, dyslexia, and early communicative behavior (Rodenas-Cuadrado et al., 2014). Such common variation in *CNTNAP2* has also been implicated in the structure and function of brain circuits relevant for language. These subtle changes have been associated with differences in gray matter volume (G. C. Tan, Doke, Ashburner, Wood, & Frackowiak, 2010; Udden et al., 2016), brain responses to syntax violations (Kos et al., 2012) and brain activation during sentence or artificial syntax processing (Folia, Forkstam, Ingvar, Hagoort, & Petersson, 2011; Whalley et al., 2011). Thus, both rare and common variation in *CNTNAP2* provides compelling evidence for a link between this gene and language-related phenotypes.

The importance of *CNTNAP2* in language-related circuitry may be related to its synaptic function. The protein produced from the *CNTNAP2* gene (called CASPR2) travels to the synapses of neurons[8] (Bakkaloglu et al., 2008) where it mediates dendritic arborization, (p. 879) spine development, and synaptic activity (Anderson et al., 2012; Varea et al., 2015). When modeled in mice, loss of mouse *CNTNAP2* resulted in reduced neurite

outgrowth, reduced activity of individual synapses, and reduced overall neural network activity (Anderson et al., 2012; Varea et al., 2015). *CNTNAP2* is not ubiquitously expressed throughout the brain, rather it is dynamically expressed (increasing in the postnatal brain) and is enriched in regions known to mediate higher order cortical functions such as cortico-striatal-thalamic circuits and perisylvian cortical regions (Abrahams et al., 2007; Alarcon et al., 2008; Gordon et al., 2016). Taken together, these data suggest that CNTNAP2 acts downstream of *FOXP2* and is required for the normal function of a subset of synapses and neural circuits which may act as part of language networks in the brain.

### 37.3.4 From genes to phenotypes—peripheral mechanisms

While the brain clearly plays the central role in language, we should not forget the means through which we perceive and produce it—hearing, seeing, speaking, and gesturing—all of which also have a genetic component. We will briefly review here aspects of the genetics of hearing loss and of the development of vocal tract structures, leaving aside vision, facial expressions, and manual gestures.

Hearing is a complex process (Stover & Diensthuber, 2011) and there are multiple causes of hearing loss, including trauma, powerful noises, infections, and normal aging, but the most interesting from a genetic (and linguistic) point of view are the various types of congenital (i.e., present at birth) non-syndromic (i.e., no other phenotypes present) hearing loss, most of them with an identifiable genetic cause (see, for example, https://ghr.nlm.nih.gov/condition/nonsyndromic-hearing-loss). Interestingly, the genetic mechanisms behind congenital non-syndromic hearing loss are multiple and sometimes surprising, highlighting the complexity of the genetic architecture of even such "external" aspects of language and speech. For example, one broad type of congenital non-syndromic hearing loss (Kokotas, Petersen, & Willems, 2007) is due to mutations in a mitochondrial gene, *MTRNR1*, that encodes a specific subunit (actually not a protein but an RNA molecule) of the mitochondrial ribosome. Certain antibiotics (such as gentamycin and streptomycin) are known to affect hearing at high doses or after prolonged exposure, but in people carrying mutations in *MTRNR1* even small doses might result in hearing loss (Bindu & Reddy, 2008; Kokotas et al., 2007) because these particular mutations make the mitochondrial ribosomes susceptible to damage from these antibiotics (Ballana et al., 2006). This example highlights several fascinating issues, including the importance of the interaction between genotype (the *MTRNR1* mutation), the individual's wider genomic background (other genes modulate the mutation's effects) and the environment (the presence of the antibiotics), and the phenotypic specificity of a mutation that affects all mitochondria (essential for energy production) throughout the body. Other interesting examples concerns recessive hearing loss (i.e., an individual needs two copies of the mutation to develop deafness). One cause of which (mutation of the *MYO15A* gene) plays a role in the structure of the stereocilia of the hearing cells (Manor et al., 2011) and resulted in the development of the emergent sign language *Kata Kolok* in the village of Bengkala, on the island of Bali, Indonesia (de Vos, 2013; A. Wang et al., 1998; Winata et al., 1995). Another cause (mutation of the DFNB1 locus involving the *GJB2* and *GJB6* genes) is implicated in the emergence of *ABSL* (Al-Sayyid Bedouin Sign Language) in (p. 880) the Negev desert, Israel (Sandler, Aronoff, Meir, & Padden, 2011). Such emergent sign languages are a very hot topic, as they may shed light on the feedback between biology and culture in language evolution and change. In brief, when recessive mutations involved in congenital hearing loss occur in communities with high rates of inbreeding or assortative mating and a good social integration of deaf members, the usual negative selective pressure against such mutations is relaxed, resulting, across

generations, in the emergence and co-evolution of, on the one hand, a sign language used by both deaf and hearing members of the community and, on the other, the increase in the frequency of the mutation (Levinson & Dediu, 2013).

Moving to the production end of speech, the development of the vocal tract is a very complex embryological process (Greene & Pisano, 2010) and we know a lot about the genetics of various pathologies such as cleft lip and palate (Dixon, Marazita, Beaty, & Murray, 2011; Leslie & Marazita, 2013), but much less is known about the genetic architecture of normal variation and its effects on speech production. Understanding the genetics and development of the vocal tract and its impact on phonetics and phonology is currently an active field of investigation bringing together phonetics (Zhou et al., 2008), computer modeling (Janssen, Dediu, & Moisik, 2015; Moisik & Dediu, 2015), various imaging techniques (Dediu & Moisik, 2016) and genetics.

## 37.4 Animal models

Several genes have now been associated with disorders that affect some aspects of speech and language via patient studies, genetic associations, and population studies. However, identifying these genes is not the end goal for language genetics. Rather, gene identification presents important new avenues for understanding the biological pathways that can bridge the gap between what is encoded in the genome and the biological readout—be it normal language or language disorder. Animal models are an invaluable way to bridge this gap since in these systems genes can be manipulated, switched on and off, or patient variants introduced to the genome and read-outs can be measured at multiple levels; molecular, cellular, neurological, and behavioral. In this way we can use cutting edge techniques to essentially survey the gene “in action,” allowing us to understand its normal function and the consequences for the organism when the gene is mutated or lost.

The complex, multicomponent system that is language is unique to humans and thus can obviously not be studied directly in animal model systems. However, it is exactly by considering language as a multicomponent system that gives us the possibility to make meaningful investigations in animal systems. If we consider some specific aspects that are shared with animals, it is not hard to start thinking of valuable ways to study shared traits and evolutionary differences. Apart from the shared genetics and neurobiology, we can consider behavioral aspects that contribute to speech and/or language such as voluntary vocal control, syntax, rhythm, vocal learning, auditory perception, speech perception, turn taking, social interactions, social communication, gesture, and so on (Fitch, 2000; Fitch, Huber, & Bugnyar, 2010; Hoeschele et al., 2015; Jurgens, 1998; Konopka & Roberts, 2016; Nottebohm et al., 1990; Taglialatela et al., 2015; ten Cate, 2014; M. J. West & King, 1988). So, while no animal encompasses all these traits, by investigating these individual traits across different (p. 881) animal models we can start to build models of key aspects that are part of language or its evolutionary precursors. Furthermore, by using animal models we can trace the biological underpinnings of these traits from the behavioral, back to the molecules and genes that are essential for their execution. In this section, we outline two examples of animal studies that illustrate this approach; the investigation of vocal learning in songbirds and stuttering in mouse models.

### 37.4.1 The genetics of vocal learning—songbirds

Vocal learning is a key component of spoken language as it is the ability to modify vocalizations by learning from others of the same species (Janik & Slater, 2000). Songbirds are one of the few species other than humans that are vocal learners and as such have been extensively studied, epitomizing the power and potential of animal models (Brainard & Doupe, 2013; Condro & White, 2014; Doupe, Solis, Kimpo, & Boettiger, 2004; Mello, 2014; Mooney, 2014; Nottebohm et al., 1990). In songbirds it has been possible to perform in depth documentation of the behavioral contexts of vocal learning and how factors such as social interaction influence this trait (Chen, Matheson, & Sakata, 2016; Kriengwatana, Spierings, & ten Cate, 2016; W. C. Liu & Nottebohm, 2007; Tchernichovski & Marcus, 2014; ten Cate, 2014; M. J. West & King, 1988). Using the zebra finch songbird, it has also been possible to map in exquisite detail the neural circuitry that underlies this behavior and differentiate the overlapping circuits and brain regions that contribute to vocal learning (anterior forebrain pathway; AFP) vs. vocal production (vocal-motor circuit) (Bertram, Daou, Hyson, Johnson, & Wu, 2014; Doupe et al., 2004; Garst-Orozco, Babadi, & Olveczky, 2014; Kubikova et al., 2014; Nottebohm, 2005). Having this neuro-behavioral framework has also made it possible to gain unprecedented insight into how genes underlie this trait in birds (Abe, Matsui, & Watanabe, 2015; Feenders et al., 2008; Heston & White, 2015; Hilliard, Miller, Fraley, Horvath, & White, 2012; Hilliard, Miller, Horvath, & White, 2012; Mori & Wada, 2015; Pfenning et al., 2014; Wada et al., 2006; Whitney et al., 2014; Whitney et al., 2015). By surveying expression changes of virtually every gene in the genome in a part of the vocal learning circuitry in behaving birds, it has been possible to build a picture of functional molecular networks that underlie singing (Hilliard, Miller, Fraley, et al., 2012; Hilliard, Miller, Horvath, et al., 2012). This revealed networks of genes that were being switched on or off in response to singing and highlighted functional pathways (such as synaptic activity) and specific genes (such as *FoxP2*) that are likely to be involved (Hilliard, Miller, Fraley, et al., 2012; Hilliard, Miller, Horvath, et al., 2012). Because it is possible to manipulate the genomes of animal models, investigations need not stop at identification, but rather can show direct involvement of genes and pathways in vocal learning. *FoxP2* is highly expressed in parts of the vocal learning circuitry in birds and it changes its expression during undirected singing (the variable “practice” phase of singing) (Teramitsu, Poopatanapong, Torrisi, & White, 2010; Teramitsu & White, 2006). It was hypothesized that *FoxP2* may be important for vocal learning in birds, as it is in humans. This proved to be the case, as when the songbird version of *FoxP2* was switched off in a key region of the vocal learning circuitry in living animals, these birds could no longer learn their song correctly (Haesler et al., 2007). This showed a direct causative link between *FoxP2* and vocal learning in birds. Further, it has been possible to bridge the gap for why *FoxP2* has this effect by investigating its role in the formation (p. 882) and activity of specific neural circuits in the songbird brain. Knockdown (reduction of expression of a gene via genetic engineering techniques) of *FoxP2* in juvenile animals leads to alteration of dendritic synapse formation (Schulz, Haesler, Scharff, & Rochefort, 2010), and in

adults *FoxP2* knockdown changes the speed of signal propagation through the vocal learning circuit by disrupting dopamine modulation of signals (Murugan, Harward, Scharff, & Mooney, 2013). Taken together, this body of work demonstrates causal links between genetic factors, neurobiology, and behavior in a way that would not be possible in the human system and shows how valuable animal models can be for understanding the biology of language-relevant traits.

## 37.4.2 The genetics of stuttering—mice

Studies of the genetics of stuttering, although still in their infancy, already tell a remarkable story of how the molecular approach can lead to a better understanding of a speech disorder and the potential for animal models to increase our understanding beyond what would be possible in human systems.

Stuttering is a speech disorder characterized by features that disrupt the smooth flow of speech including blocks (hesitations or pauses) and frequent repetition or prolongation of syllables—most often at the beginning of words or sentences (Seery, Watkins, Mangelsdorf, & Shigeto, 2007; E. Yairi, 2007; Ehud Yairi, Watkins, Ambrose, & Paden, 2001). Although many twin, family, and adoption studies clearly indicated that stuttering has genetic causes, for a long time these causes were obfuscated by unclear modes of inheritance and the lack of any strong candidate genes (Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Felsenfeld et al., 2000; Kraft & Yairi, 2012; Newbury & Monaco, 2010; Viswanath, Lee, & Chakraborty, 2004). However, in 2010, mutations in a gene known as *GNPTAB* were identified in a large inbred family with recurrent stuttering (Fisher, 2010; Kang et al., 2010). Mutations in this same gene were then identified in unrelated stutterers, but rarely in the general (non-stuttering) population, suggesting that mutation of this gene was a cause of stuttering (Drayna & Kang, 2011). However, mutations in this gene could not account for most known cases of stuttering, and so in a move that perfectly illustrates the power of the molecular approach, the researchers turned to a molecular understanding of this gene to find further causes of stuttering. It was already known that *GNPTAB* encoded a protein that functioned in the lysosomal enzyme targeting pathway (involved in the degradation of cellular products) and this pathway was well characterized (Drayna & Kang, 2011; Reitman & Kornfeld, 1981). Thus, it was possible to identify other members of this pathway and ask if they are also candidates for stuttering. Strikingly, these predictions proved correct and mutations in two closely related genes that act in this pathway, *GNPTG* and *NAGPA*, were found in stutterers, but not in the general population (Drayna & Kang, 2011). Highly destructive mutations in these genes (e.g., that completely destroy the protein product) cause a group of severe metabolic disorders that are lethal in early life with widespread pathology affecting cognition, bone development, connective tissue, eyesight, organ function, and so on (Kudo, Brem, & Canfield, 2006; Raas-Rothschild et al., 2000). Despite carrying mutations in these same genes, people who stutter generally display no other impairments in cognitive, motor, or language tasks (Drayna & Kang, 2011; Kang et al., 2010; Raza et al., 2016). This discrepancy is thought to be due to the type of mutation found in stutterers, **(p. 883)** which unlike the destructive mutations found in metabolic disorders, represent subtle, often single letter changes to the protein sequence (Drayna & Kang, 2011; Kang et al., 2010; Raza et al., 2016). In total, mutations in these three genes now account for up to 16% of all cases of stuttering (Drayna & Kang, 2011; Kang et

al., 2010; Raza et al., 2016), providing convincing evidence that this pathway contributes to speech and its disruption leads to the stuttering speech disorder.

The clear link between the lysosome targeting pathway and speech/disorder presented a conundrum because these genes are expressed, and this pathway is active, in every cell in the body. So how do mutations in a very general process result in a highly specific phenotype- like stuttering? Investigating why lysosomal targeting pathways affect specific neural circuitry affecting speech represents a major challenge in humans, making animal models an attractive alternative. Although mice do not speak, they do exhibit high homology with the genetics and neurobiology of humans and use vocalizations to communicate (Arriaga, Zhou, & Jarvis, 2012; Fischer & Hammerschmidt, 2011; Holy & Guo, 2005). Thus, studying links between the lysosomal targeting pathway and vocal production becomes a tractable neuro-molecular question when asked in mice. Just like in humans, complete loss of these genes causes widespread pathology and lethality in mouse models, but when one of the patient-identified mutations in *GNPTAB* was introduced in mice, much more subtle vocal related effects were observed (Barnes et al., 2016; Idol et al., 2014; Paton et al., 2014). Mice carrying the patient mutation in *GNPTAB* produced significantly fewer vocalizations than normal mice due to significantly longer pause lengths between bouts of vocalizing (Barnes et al., 2016). Furthermore, these mice displayed reduced diversity in sequencing of syllables and more stereotyped vocalizations (Barnes et al., 2016). Although this doesn’t exactly recapitulate human stuttering, it does show similarities with the human phenotype as human stutterers show speech characterized by frequent repetitions of syllables, fewer vocalizations, and longer pauses between vocalizations (Barnes et al., 2016; Seery et al., 2007; E. Yairi, 2007). The phenotypic similarity observed between humans and mice carrying the same mutation now presents a superb opportunity to understand how this genetic mechanism leads to normal and disrupted neurobiology underlying vocal production. It will be of great interest to see what we learn from this animal model in the future that can be applied to our understanding of the molecular and neurobiological underpinnings of both stuttering and normal speech in humans.

### 37.4.3 Animal models—concluding remarks

An important consideration with animal models is to choose the right animal system for the question under study. For example, mice are strong genetic models with sequenced genomes and relatively easy methods for switching off genes in whole organisms, tissues, or even specific brain circuits—however they are not vocal learners (Hammerschmidt et al., 2012; Kikusui et al., 2011; Mahrt, Perkel, Tong, Rubel, & Portfors, 2013). By contrast songbirds are extremely good vocal learners and while they do have a sequenced genome it is still extremely difficult to produce genetic manipulations, limiting the volume and speed by which genetic mechanisms can be studied (Velho & Lois, 2014). To understand the full range of language-relevant traits we must use a range of animal systems considering the strengths of each. In summary, multidisciplinary investigations into complementary animal models at (p. 884) genetic, neurological, and behavioral levels are essential if we are to understand how genetic factors functionally program the biological components relevant to language and translate this knowledge back to the human system.

## 37.5 Discussion and conclusions

This chapter has now covered the basic principles of the genome, how complex molecular mechanisms control genes to produce language-relevant neuronal and behavioral phenotypes and how we can study models from the basic cell in a dish to complex animal systems to bridge the gap between genes and language. But before ending, we must return to the third principle highlighted in the introduction, namely that “no matter how much we will know about the genetic bases of language and speech we must never forget the cultural side of this evolutionary spiral.” Language is intrinsically a chimera with both a biological component (rooted in genetics) and a sociocultural component, locked in a complex dynamics of co-evolution. It is unquestionable that language is a full cultural evolutionary system in its own (Dediu et al., 2013; Pagel, 2009) and that we must understand language evolution and change, and the resulting patterns of diversity and cross-linguistically shared properties in this framework. However, we must not lose sight of the fact that language is not a purely cultural phenomenon, evolving somehow detached from the biology of its users and the environment they inhabit, but that these extralinguistic factors (genetics being a major—even if indirect—one) generate forces (strong or weak) that shape the constraints and affordances to which language adapts (Bickel et al., 2015; Christiansen & Chater, 2008; Dediu, 2011; Everett, Blasí, & Roberts, 2016; Levinson & Dediu, 2013). In turn, language must have generated strong enough pressures on our genome that explain the various adaptations we seem to possess for producing, perceiving, processing, and acquiring language, but, more importantly, language is a major component of our uniquely impressive capacity for cumulative cultural evolution (Richerson & Boyd, 2005) and cultural niche construction (Kendal,

Tehrani, & Odling-Smee, 2011; Odling-Smee, Laland, & Feldman, 2003) that, in turn, shaped and still shapes our genome (Dediu et al., 2013; Fisher & Ridley, 2013; Gerbault et al., 2011).

We hope that this brief review has managed to kindle interest in this fascinating, dynamic, and complex scientific endeavor that aims at unraveling the genetic foundations of language, and that the pointers to the literature we have provided will offer an accessible entry point in this dense, technical, and multidisciplinary literature. We hope to see the readers of this chapter contributing to the future breakthroughs that will better bridge the "lower-level" approaches using molecular techniques, cell lines grown in dishes, and various animal models, with the "higher-level" aspects of human language better captured by the language sciences and the cognitive neurosciences.

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## Notes:

([1]) Throughout this chapter we use “culture” in its technical sense of socially learned information shaped by evolutionary processes and various types of biases (e.g., Dediu et al., 2013; Richerson & Boyd, 2005); language then is a type of culture, and applying concepts and methods from, among others, Cultural Evolution, Gene-Culture Co-evolution, Cultural Niche Construction, and Iterated Transmission, helps understand how language emerged, changes and diversifies, as well as its multiple interactions with non-linguistic factors (Dediu et al., 2013; Dediu, Janssen, & Moisik, 2017).

([2]) Sign languages are another fascinating case that we will only briefly touch upon here, but see for example Dediu (2015) for a discussion of the genetics of hearing loss and emergent sign languages.

([3]) Importantly this is also a generalization. There are many different types of neurons and each of these employs its own unique “reading” of the genetic code.

([4]) Following the guidelines on gene nomenclature, in this chapter human and primate gene symbols are italicized and in upper-case (*FOXP2*), rodent gene symbols are italicized with only the first letter in upper-case (*Foxp2*), and other species in upper and lower (*FoxP2*). Protein names are not italicized (FOXP2/Foxp2/FoxP2) (Kaestner, Knochel, & Martinez, 2000; Maltais et al., 2002; Wain et al., 2002).

([5]) Each human cell contains 23 pairs of chromosomes, one of each pair is transmitted from each of the parents.

([6]) This view is an approximation of what is postulated to happen at molecular level. Other factors should be taken into account contributing to accessibility and chemical interaction between proteins and DNA (Bulut-Karslioglu et al., 2012; Lawrence, Daujat, & Schneider, 2016; Saksouk, Simboeck, & Dejardin, 2015).

([7]) Although it is debated what non-word repetition tasks measure (e.g., phonological memory, motor programming, and so on), deficits in this task are a core feature of a range of language impairments and often used in diagnostic criteria.

([8]) The CNTNAP2 protein is also found in other places including parts of myelinated nerves (Poliak et al., 1999, 2001).

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