Looping Genomes: Diagnostic Change and the Genetic Makeup of the Autism Population[1]

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This article builds on Hacking's framework of "dynamic nominalism" to show how knowledge about biological etiology can interact with the "kinds of people" delineated by diagnostic categories in ways that "loop" or modify both over time. The authors use historical materials to show how "geneticization" played a crucial role in binding together autism as a biosocial community and how evidence from genetics research later made an important contribution to the diagnostic expansion of autism. In the second part of the article, the authors draw on quantitative and qualitative analyses of autism rates over time in several rare conditions that are delineated strictly according to genomic mutations in order to demonstrate that these changes in diagnostic practice helped to both increase autism's prevalence and create its enormous genetic heterogeneity. Thus, a looping process that began with geneticization and involved the social effects of genetics research itself transformed the autism population and its genetic makeup.

It is by now well recognized that most traits and disease categories do not line up in a straightforward way with characteristics of the human genome (Lock 2005; Wade 2009). Nevertheless, the project of explaining, tracing,

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or even defining categories of human difference at the level of the genome continues apace. There remains widespread hope that knowledge about genetic variants will allow researchers to unlock the biological basis of disease, leading to novel forms of treatment and a more biologically grounded nosology in fields like psychiatry (Collins et al. 2003; Insel 2013). Meanwhile, studies seeking genetic correlates for delinquency and aggression (Buckholtz and Meyer-Lindenberg 2008; McDermott et al. 2009; Simons et al. 2011), educational attainment (Shanahan et al. 2008; Rietveld et al. 2013), and other sociologically pertinent categories are enjoying a significant resurgence, even if most such studies emphasize the role of gene × environment interaction (e.g., Guo, Tong, and Cai 2008; Schnittker 2008; Daw et al. 2013; for reviews, see Bearman 2008; Freese and Shostak 2009; Conley, Fletcher, and Dawes 2014).

This "postgenomic" consensus, which adopts a more measured understanding of genetic influences on human health, illness, and difference, challenges sociologists to develop new ways of understanding the social consequences of genetics research. If there is no underlying "gene-for" most of the categories of human difference we know and care about, how can we make sense of the continuing efforts to understand the complex genomic correlates of human disease, difference, and ancestry? Against the backdrop of this systemic uncertainty about the relationship between genotype and phenotype, neither Lippman's (1991*a*, 1991*b*) warning of a reductionist "geneticization" nor Rabinow's (1992) celebration of a new "biosociality" seems sufficient as a guide to understanding the social consequences of genetics research. In this article, we present a sociological framework for understanding the findings emanating from the fields of human and medical genetics as neither timeless "facts" nor social constructions but as mobile elements in a dynamic process. We show how ideas and evidence about genetic etiology affect the classification of disease and difference, even as the resulting changes in disease classification transform the scope for identifying genetic mutations in the population that is diagnosable with a given condition. Put differently, as the categories through which we diagnose disease shift over time (see, e.g., Fleck 1981; Rosenberg and Golden 1992; Aronowitz 1999), sometimes in interaction with knowledge about their genetic makeup, so too do findings about what we take genetic abnormalities to be etiological for.

To demonstrate the plausibility of these arguments, we bring what Hacking (1995, 1998, 2007) has called "looping" into dialogue with human genetics

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and examine the instructive case of autism—a human kind, as Hacking himself argued, that is "doubtless biological, . . . [yet] nevertheless has been wandering" (Hacking 1995, pp. 374–79; 2006*b*; Nadesan 2005; Eyal et al. 2010). Hacking and others, as we explain in greater detail in the next section, have documented the way looping processes cause classifications, practices, and the "kinds of people" who are classified to recursively change one another over time, sometimes quite dramatically. We adapt that framework by entering both the results of genetics research and the genetic composition of the populations that comprise kinds of people into the mix of elements that can effect change and be changed through looping processes. But how could we demonstrate that a looping process changed the genetic makeup of the autism population over time? After all, it is impossible to observe the genetic heterogeneity of autism over time by looking at genetic studies conducted on autism patients—genetic testing techniques have changed too much and, with few mutations accounting for more than 1% of caseloads, even the largest research cohorts are too small to gain any statistical power on their incidence in the autism population over time.

We circumvent this problem by going in the other direction: examining the rates of autism diagnoses in research cohorts selected on the basis of specific genetic mutations. Since 1959, the human genetics literature has reported hundreds of such studies on "genomically designated" conditions like fragile X, 5p minus, and Phelan-McDermid/22q13 deletion syndrome that are delineated strictly according to genetic mutations (Navon 2011, 2013). By examining the history of research on people with these genomically designated conditions, we can effectively control for genetic etiology and examine changes over time in the medical problems and traits that these mutations are understood to cause. If we see that rates of autism in cohorts of genomically designated subjects have risen consistently, often from nonexistent to quite high, then we can reasonably claim to have shown that autism has absorbed new genetic mutations into its ranks because of diagnostic change. In so doing, we provide confirmation of the finding that diagnostic expansion contributed to autism's enormous rise in prevalence (Shattuck 2006; King and Bearman 2009; Eyal 2013): even when we hold the genetic cause of developmental difference constant, changes in diagnostic practice considerably increased the number of people with autistic spectrum disorders (ASDs). Later in this article, we present quantitative and qualitative evidence in support of this hypothesis.

By itself, this finding could be narrowly interpreted—after all, it is hardly surprising that when diagnostic criteria are modified and the population so delineated changes accordingly, its genetic makeup changes as well. This narrow interpretation could be operationalized as the null hypothesis that diagnostic expansion increased the risk of an ASD diagnosis evenly throughout the population and that the increase in genetic heterogeneity was there-

fore just the random accrual of genetic variants. This is not, however, what our findings indicate. While it is plausible that there has been an increase in the number of common variants associated with autism, very few such associations have been reported in the literature, and most of those could not be replicated (Anney et al. 2012, pp. 4783–84; see also Betancur, Sakurai, and Buxbaum 2009, p. 408; Betancur 2011, p. 63). In short, there are no data with which to test this null hypothesis. Our findings, which draw on decades of published research in human genetics, speak to an altogether different process. The genetic disorders we analyze are rare, and the underlying mutations are typically highly penetrant. They have long fascinated human geneticists without, until recently, being linked to autism. Crucially, as we show below, they go from little or no association with ASDs to rates that, given ASD prevalence, are orders of magnitude higher than could be possible for any common genetic variant. In other words, this is not a story about autism rates rising evenly throughout the population but a dynamic process in which genetic evidence helped to steer autism's diagnostic criteria toward a set of populations that have been understood for at least the last century or so as suffering from some form of hereditary/genetic abnormality. The plausibility of this interpretation will be bolstered by a historical narrative and a few detailed case studies that show that diagnostic change was the product of complex looping processes in which ideas and evidence about genetic etiology themselves played a vital role. Evidence that autism is a genetic condition (1) modified how individuals with autism (and their parents) understood themselves and were understood and treated by others in ways that contributed to a massive increase in caseloads and (2) was mobilized in favor of diagnostic expansion. As we will see, our understanding of autism as a heritable, genetically heterogeneous condition has been at once a driver and an outcome of looping processes.

This article consists of five sections and a conclusion. The first adapts Ian Hacking's looping framework to show how human genetics can enter into a dynamic interaction with shifting practices of medical classification. In the second section, we discuss the puzzle presented by contemporary autism genetics and argue for a historical approach to supplement existing attempts to solve it. In the third, we present a historical analysis of the "geneticization" of autism as a series of four loops leading to diagnostic expansion, increased prevalence, and genetic heterogeneity. The fourth section delves into the foundational association between autism and fragile X syndrome in order to outline the "conditions of possibility" for autism's genetic heterogeneity. In the fifth section, we present quantitative and case study evidence that the association between a series of genomically designated conditions and autism has radically increased over time, thus supporting our argument that looping processes transformed the genetic makeup of the autism population.

HUMAN KINDS AND THE HUMAN GENOME

Hacking's framework of "dynamic nominalism" (1995, 1998, 2006*a*, 2007) has informed a range of work in the social studies of science and medicine. He has provided a succinct definition: "People classified in a certain way tend to conform to or grow into the ways that they are described; but they also evolve in their own ways, so that the classifications and descriptions have to be constantly revised" (Hacking 1998, p. 21). The argument is composed of two steps: the first, familiar to sociologists at least since "labeling" theory (Becker 1963), is that classifications shape the identities and ways of acting of the individuals to whom they are applied. These classifications can thereby bring a new "human kind" (Hacking 1995) or "kind of person" into being (Hacking 2007). The second and more innovative part of the argument is that the actions of the kinds of people thus created often defy expert expectations, transgress the content of the classification itself, and therefore loop back to reshape diagnostic classifications, rendering them continuously moving targets (Hacking 2007).

At first glance, it might seem as though this argument only applies to the looser "psy" categories (Rose 1998) like multiple personality disorder (Hacking's [1995] most fully fleshed out example), while classifications that are affixed to biomarkers and especially genetic mutations should not loop in the same way. Indeed Hacking (1995, p. 352) once wrote that "quarks, probably genes, possibly cystic fibrosis" are natural kinds.[2] Labeling them as such does not, by itself, affect their behavior. At the same time, Hacking (1995, p. 372) argued that "biologizing human kinds does not thereby make them immune to looping effects." Simply put, his point was that while a gene might be a natural kind, a person with a gene is a human kind; while the gene may work the same way before and after being labeled, telling people that they have a gene for cystic fibrosis or some other condition and treating them on that basis is another matter entirely. Yet, Hacking failed to develop this argument. He gave the example of how "the scientific (biological) knowledge about alcoholics *produces a different kind of person*" (p. 373; our emphasis) but did not explicate how the actions of this kind of person might loop back to modify the classification and scientific knowledge about it.

In this article, we continue where Hacking left off and demonstrate not only how the ascription of genetic etiology to kinds of people can "produce a different kind of person" but also how the actions undertaken by this new kind of person can loop back to change the findings of genetic research. This requires introducing two modifications to Hacking's looping model: the first is that findings from genetics research can change the way people

[2] Hacking later sided with the school of thought in philosophy that rejected the concept of natural kinds altogether, leading him to abandon the term "human kind" for the more straightforward "kind of person" (2007, n. 17).

with an existing classification understand themselves and are understood and treated by others. This can happen, for example, because "by and large, biology is exculpating" (Hacking 1995, p. 373); the discovery of genetic etiology can remove stigma or the attribution of blame (see Phelan 2005; Shostak, Conrad, and Horwitz 2008, for more nuanced accounts). This destigmatization through biologization is intuitively easy to grasp, and later in this article we see how something similar happened in the case of autism. Yet we will also argue that destigmatization is only one—and not necessarily the most important—of the many ways in which the imputation of genetic etiology can reshape human kinds. For example, we will see how ideas and evidence about genetic etiology allowed parents (and researchers allied with parents' organizations) to interpret and leverage the imputed similarity between themselves and their children to change autism into a continuum of impairment and difference. Genetics research, in short, can help to change the way a population is delineated and understood and thus play a role in the looping processes that make and remake kinds of people over time.

The second point is that changes in diagnostic practice can reconfigure the distribution of genetic mutations to be found in the population captured by the classification in question. In other words, every time diagnostic criteria are changed—whether to better capture phenotypic variability, to better reflect/validate genetic evidence, or for any other reason—the genetic makeup of the population picked out by the now-changed classification may also be modified. This new population changes the material conditions for examining the genetic etiology of the classification, which in turn can modify expert understandings of the condition and thereby the self-understandings of the people picked out by the classification. When human kinds loop, their genetic makeup can also therefore be rendered a moving target. The more general point is that the effects of genomic difference (de novo mutations, inherited gene alleles, or what have you) are mediated by the shifting, socially embedded categories that are used to diagnose disease and classify human difference. In the case of autism, we will see how evidence from genetics research and classificatory practices changed one another through looping processes, reshaping the category of autism and bringing it into strong associations with a series of previously unrelated, rare, and highly penetrant genetic mutations.

A final clarification is necessary to dispel a reductionist interpretation of our argument. Because looping involves lay actors and their awareness of being classified, it could be taken as implying that diagnostic categories are "false" because they are shaped by social factors rather than objective research alone. That is emphatically not our argument, and indeed Hacking deployed the term "dynamic nominalism" in large part to reject the opposition between what is real (and therefore supposedly immutable) and

what is merely a name or a social "construction" (and therefore ephemeral; see esp. Hacking 1995, 2007). Showing that diagnostic classifications loop because people are aware of being classified does not make the classifications and the kinds of people they designate any less real. In analyzing the complex looping process described in this article, we therefore treat diagnostic categories neither as "natural kinds" that carve nature at its joints nor as mere social conventions but as discursive statements that have precise conditions of possibility (Foucault 1977, 2002; Latour 1987). These conditions are heterogeneous and historically changing. They involve elements of what in other approaches are distinguished as material, technical, institutional, and "social" but are here all treated symmetrically as conditions enabling and restricting what can be said, seen, and manipulated. As such, when we argue that diagnostic categories changed because of looping, or that diagnostic change led to further looping, this is an argument about how statements about the genetic makeup of the autism population have developed historically, not an attempt to expose the illegitimate influence of social factors on the process of scientific discovery. When it comes to the classification of human difference, there are no categories to be found or knowledge to be had (biological or otherwise) that are independent of their conditions of possibility or immune from looping effects.

DISSOLVING THE PUZZLE OF AUTISM GENETICS

Our point of departure is a modified version of the "intriguing puzzle" presented by Liu, Zerubavel, and Bearman (2010, p. 327) that draws our attention to several widely accepted, yet seemingly contradictory, biomedical facts about autism.

Biomedical fact 1.—The prevalence of autism has increased rapidly and substantially over the last four decades from 4 in 10,000 in 1989 to 1 in 68 American 8-year-olds (Kogan et al. 2009; Baio 2012; Baio et al. 2014).

Biomedical fact 2.—Autism is strongly genetically determined. Indeed, "Autism has the highest estimated heritability (≥90%) among behaviorally defined neuropsychiatric disorders" (Brkanac, Raskind, and King 2008, p. 599; see Nordenbæk et al. [2013] for a recent twin study that puts ASD heritability at approx. 95%). While recent studies using larger sample sizes and employing more sophisticated models of heritability estimation have put the figure considerably lower than 90%, it remains the case that autism is considered one of the most heritable neuropsychiatric disorders (Liu et al. 2010; Hallmayer et al. 2011; Gaugler et al. 2014; Colvert et al. 2015).

These first two observations stand in considerable tension with one another because fundamental changes in the human gene pool in such a short period of time have never been observed and, theoretically, should be impossible. How then could a highly genetic disorder grow in prevalence by

more than an order of magnitude? One possible answer is that autism is caused by some kind of gene-environment interaction and that rapid changes were taking place in the environment, not in the gene pool. However, the third observation complicates any putative gene-environment explanation of increased prevalence considerably.

Biomedical fact 3.—No fewer than 179 rare, mostly highly penetrant genetic mutations (124 single gene mutations and 55 chromosomal anomalies) and counting have been associated with autism. None of those 179 mutations accounts for more than 1%–2% of caseloads, and most considerably less. As yet, no common genetic variants have been consistently found to be associated with autism (see below; Abrahams and Geschwind 2008; Betancur 2011; Pinto et al. 2014).[3] Only around 15%–25% of autism caseloads are attributable to these anomalies (Miles 2011, p. 282; Berg and Geschwind 2012; Carter and Scherer 2013).

This means that an explanation of the autism epidemic must also explain its genetic heterogeneity, or at least how environmental changes could operate in a similar way on this highly heterogeneous genetic population. Until now, only Liu et al.'s (2010) demographic argument hypothesizing an increase in de novo mutations as a result of increased average parental age has presented such a mechanism. This mechanism, however, can only account for a small fraction of autism's increased prevalence (Peter Bearman, personal communication).[4] However, even if demographic factors

[3] While a recent paper reported a higher contribution of common genetic variation to total autism caseloads than previous studies (Gaugler et al. 2014), it did not identify actual common variants that have significant associations with ASDs. Furthermore, its exclusion criteria eliminated precisely the kind of patients most likely to have one of the rare mutations that are highly penetrant for developmental deficits and strongly associated with autism. As a 2012 study written by several of the same authors explains, despite extensive efforts by researchers, only a handful of SNPs (single nucleotide polymorphisms) or other common genetic variants have been associated with autism, and none of those associations have been replicated in subsequent studies (Anney et al. 2012, pp. 4783–84; see also Betancur et al. 2009, p. 408; Betancur 2011, p. 63). As the paper's senior author, Joseph Buxbaum, has discussed in other recent work, "common polymorphisms have so-far proven difficult to identify and replicate. . . . In contrast, a focus on rare and *de novo* mutation has already been highly productive in uncovering an appreciable fraction of population risk conferring larger biological effects" (Buxbaum et al. 2012; see Brandler and Sebat [2015] for a more recent discussion of this point). In short, when researchers discuss autism's observed genetic heterogeneity, they are almost exclusively referring to rare, highly penetrant, and often de novo variants of the kind we focus on in this article.

[4] Liu et al. compare same- and opposite-sex twin pairs' concordance for autism in a large data set of California children between 1992 and 2000. Because 0% of opposite-sex twins are monozygotic (MZ), compared to just over half of same-sex twins, population-level data about births and sex can be used to generate reliable estimates of the number of MZ vs. DZ (dizygotic) twins. Using this method Liu et al. estimate that autism's heritability is much lower than the estimates generated by small-*n* twin studies (they put it at 19% for males and 63% for females), but they also provide evidence that autism's heritability actually increased between 1992 and 2000. They ascribe this extraordinary population

did lead to an increase in the population rate of genetic mutations that can cause autism, a fourth observation imposes a new requirement that cannot be explained by an aggregate increase in the incidence of these mutations.

Biomedical fact 4.—Not only is autism genetically heterogeneous, but all of the mutations associated with it can also cause intellectual disability (ID) or other developmental disorders (Laumonnier et al. 2004; Marshall et al. 2008; Betancur 2011; Pinto et al. 2014). From a genetic point of view, there is "absence of clarity surrounding the specifics of the relationship between ASDs, MR [mental retardation] and other neuropsychiatric disorders" (Abrahams and Geschwind 2008, pp. 352–53).

Given their common genetic basis, an increase in autism-causing mutations in the population should have led to comparable increases in the prevalence of ID as well. However, it is well established by now that there has in fact been a slight decrease in ID prevalence alongside a large spike in autism caseloads (Boyle et al. 2011). Special education enrollments under the eligibility category of mental retardation (MR) declined from 1994 to 2003 (Shattuck 2006), and there is compelling evidence of diagnostic substitution from MR/ID to autism (Bishop et al. 2008; King and Bearman 2009). This is a problem not only for the demographic explanation but also for any environmental explanation of increased autism prevalence: whether through gene-environment interaction, epigenetic effects, or an increase in de novo mutations, there is simply no plausible mechanism reported in the literature, even speculatively, that can explain the divergent prevalence trends of ID and ASDs given their remarkably similar genetic bases. The point is not that demographic or environmental explanations are wrong but that they cannot by themselves explain why these children were diagnosed with autism rather than ID or other related developmental disorders.

In this article we introduce a looping mechanism that can account for the way the same genetic mutations confer dramatically different risks of ASD diagnoses for their bearers over time. By examining this looping mecha-

change to an increase in de novo genetic mutations due to a demographic increase in average parental age. To foreshadow, we think this explanation is in large part correct: de novo genetic mutations probably do account for much of this increase in autism's heritability. We disagree with Liu et al., however, when they specifically rule out changes in diagnostic practice as a mechanism for this trend (2010, p. 340). Our evidence cannot speak to whether there was an increase in the rate of de novo mutations in the population as a whole. Instead, we show that over the last three decades a host of rare genetic mutations (a significant minority of which are not de novo but inherited), which were already known to geneticists, became strongly linked to autism. Furthermore, we show that ASD rates in bearers of these rare mutations have increased far more rapidly than in the general population. Liu et al. are probably right that an aggregate increase in de novo mutations led to increases in the prevalence and heritability of autism, but the effect size of that mechanism is driven largely by the fact that, today, looping has made it far more likely that the bearers of these genetic mutations will be diagnosed with autism.

nism, we explain, and thereby dissolve, the seemingly contradictory nature of the four points above. Consider the well-established observation: autism's increased prevalence is, at least in large part, the result of diagnostic expansion (Frith 2003; Shattuck 2006; Grinker 2008; King and Bearman 2009; Eyal et al. 2010; Eyal 2013).

This observation can help explain the next two pieces of the puzzle: (1) Estimates of autism's heritability based on small-*n* twin studies increased over time (see below; cf. Folstein and Rutter 1977*a*, 1977*b*, and Bailey et al. 1995) because diagnostic expansion increased the proportion of monozygotic twins who could be given concordant ASD diagnoses. Indeed, we show below how evidence that a broader definition of autism constituted a more heritable phenotype reinforced the move toward diagnostic expansion from the late 1970s onward. (2) Autism's genetic heterogeneity also increased as a result of diagnostic expansion: that is, the number of genetic mutations associated with autism grew over time because broadening diagnostic criteria brought populations with highly penetrant genetic mutations into the ASD fold at a much higher rate than the rest of the population. To be clear, our argument is that people with the same mutations are now more likely to be diagnosed as autistic than they were in years past, net of environmental factors, epigenetic effects, and demographic changes.[5]

Finally, the fourth piece of the puzzle no longer poses a problem: even though they are associated with the very same genetic mutations as autism, the prevalence of conditions like MR/ID did not increase because people bearing those mutations have been understood for decades to be at high risk for MR/ID diagnoses. By contrast, people with those mutations only began to be diagnosed with ASDs at high rates once diagnostic criteria were substantially changed.

In short, a historical explanation based on looping can reconcile prima facie contradictory biomedical and epidemiological facts about autism. The rest of this article is dedicated to presenting and empirically validating such an explanation.

[5] This part of our argument is similar to Boardman, Blalock, and Pampel's (2010) demonstration that the genetic heritability of smoking behavior changed over time due to social processes. However, the behavioral outcome in our case is an autism diagnosis. The risk of a diagnosis is composed of a variety of factors—some of them genetic, some environmental, and some having to do with processes of ascertainment. When diagnostic criteria changed and lead to increases in the genetic heterogeneity of autism, they may have therefore changed the relative genetic influence on the risk of an autism diagnosis. As we see below, broader diagnostic criteria led to higher heritability estimate from small-*n* twin studies, and Liu et al.'s finding of increasing ASD heritability is based on data from a period of rapid diagnostic expansion. Diagnostic change—as well as other factors we describe—may be analogous to the social trigger and social push mechanisms discussed by Boardman et al. (2010, pp. 2–3).

AUTISM, GENETICS, AND LOOPING

In this section, we present a schematic account of four "loops" that transformed autism over the last 70 years from a rare disorder with "cardinal symptoms" into an increasingly prevalent, heritable, and genetically heterogeneous spectrum of communicative and social deficits. A key feature of our account is that we focus on the role that "geneticization"—the process by which a condition or trait comes to be understood as primarily caused by faulty genes (Lippman 1991*a*, 1991*b*)—played in these loops. Previous accounts of the geneticization of autism have focused either on the reductionism it entails, how it "narrow[s] both professional and lay perspectives" (Bumiller 2009, p. 880), or on the biosocial communities to which it gave rise (Singh et al. 2009; Singh 2010; Silverman 2011, pp. 141–66; Tabor and Lappé 2011). While our account owes a great deal to Silverman's and Bumiller's perceptive analyses, it is the only one to consider the dynamic interplay between geneticization and the biosocial identities it produces. We build on Silverman's account to show that genetics served to reinterpret the ties between autistic children and their parents, thereby destigmatizing autism parenting and knitting together a biosocial community. However, we also consider how the activism and advocacy undertaken by this community modified the material underpinnings of genetics research. Like Bumiller, we pay special attention to the moment in the late 1970s when the results of genetics research decisively validated the claim that autism was a genetic disorder, but we also show that these results were mobilized in support of the drive to expand autism's diagnostic criteria, thereby increasing its genetic heterogeneity and rendering the genetics of autism a moving target.

Loop 1: Kanner and the Parent-Child Dyad

When Leo Kanner first reported the existence of autism in 1943, he described an extremely rare disorder characterized by "profound aloneness," insistence on sameness, and "islets of ability." Kanner's formulation brought a new "human kind" into being that did not previously exist (Hacking 2006*a*; Eyal et al. 2010). Individuals exhibiting symptoms that we would call autistic today would not have been able to describe themselves using the language of autism and were most likely treated by others as "feebleminded" or schizophrenic.

Autism might seem an unlikely case of looping because the people classified—children with autism—are unable, due to their age and disability, to become aware of being classified. Yet, as Hacking (1995, p. 374) argued, even in the absence of such self-awareness, "there can be looping that involves a larger human unit, for example the family." The parents of these children certainly can become aware of the classification and act on its basis in ways that loop back to modify it. Moreover, if the classification does not

only pick out the children but also implicates the parents as sharing the same condition, or as having caused it, or both, the parents will be even more likely to act on this knowledge. This is precisely what happened in the case of autism.

Kanner observed 11 children who, he reported, "have come into the world with innate inability to form the usual, biologically provided affective contact with people" (1943, pp. 135–36). Yet, a few years later he also noted how "the children have been brought up in emotional refrigerators . . . [lacking] the warmth of genuine parental affection" and spoke of the children as having "removed themselves" from the world in response to this atmosphere (Kanner 1949, p. 27). In retrospect it seems as if Kanner could not decide between a psychogenic or biogenic theory of causation. For Kanner, however, who was first and foremost a clinician, the two statements were not necessarily contradictory but intimately related to a third observation that he repeated often and of which he seemed quite sure: the parents, although normal, resembled their children in telltale ways. The parents were highly intelligent but also obsessive and cold: "The parents, grandparents, and collaterals are persons strongly preoccupied with abstractions and limited in genuine interest in people" (Kanner 1943, p. 135). This observation has become received wisdom about autism to this day—however many times it has been refuted (Allen et al. 1971).

This new human kind therefore applied not just to the diagnosed individual, but to a dyad—the autistic person and the "autism parent" bound together not only through kinship but also through this similarity imputed by Kanner.[6] This similarity could be interpreted as causative (cold parenting creates autistic children) or as a correlation reflecting a third factor (constitution, genes, etc.). While the parents rejected the imputation of causation, we will see how an important contingent of parents embraced the genetic interpretation of similarity and turned it into an important basis for their self-knowledge and actions.[7] We should underline the importance of this point. Autism today is a spectrum disorder running the gamut from profound retardation to near normality, but it was decidedly not such a spectrum disorder for Kanner. As we will see, it is impossible to understand

[6] Actually it is a triad because there are important differences between the positioning of fathers and mothers within the human kind. Unfortunately, we cannot develop this point any further within the scope of this article.

[7] We do not mean that parents received a formal diagnosis of autism. The phenomenon of parents receiving a formal ASD diagnosis after their children were diagnosed is a relatively recent development and seems to be mostly driven by the layperson's interest in the diagnosis. Put differently, the "engine of medicalization" in this case is lay, rather than professional, interests (Conrad 2005). We mean, rather, the widespread notion, in both clinical and lay circles, that parents exhibit subclinical "autistic traits" (see, e.g., Ciaranello and Ciaranello 1995, p. 102), a notion that has recently been formalized in a diagnostic instrument measuring an "autism quotient" (Baron-Cohen et al. 2001).

how autism could morph into a spectrum without taking into account the way the classification also indexes the parents and identifies them as similar to their children. Given the many transformations the diagnosis of autism has undergone since Kanner, perhaps the most stable fact about it is that it names a dyad of parent-child and forges a bond of similarity between them that goes beyond the normal affinity of family. This bond may be interpreted in different ways—indeed, the looping processes depicted below have modified its meaning considerably—yet it has persevered as the most distinctive characteristic of this human kind.

Loop 2: Rimland and Geneticization

The geneticization of autism did not originate in a scientific research program but from the struggles of parents of children with autism against the prevailing psychogenic theory and the stigmatizing notion of the "refrigerator mother." It was the father of an autistic boy, Bernard Rimland, who wrote the first work arguing that autism was a genetic disorder (Rimland 1964), precisely in order to dispatch the psychogenic explanation of autism. To this end he mobilized a great deal of evidence in support of a genetic explanation. This move toward geneticization initiated a spiral of looping with unforeseen consequences. With hindsight, we can appreciate the irony that Rimland (pp. 52, 59–60) actually insisted that autism was rare because he thought rarity constituted evidence that it was genetically determined. If cold parenting caused autism, he reasoned, the diagnosis ought to be much more widespread and should come in gradations, as in a spectrum. But autism was rare, Rimland argued, and "there is an absence of gradations of infantile autism which would create 'blends' from normal to severely afflicted" (p. 52).

Yet by geneticizing autism, Rimland helped to set in motion looping processes that led it to become both widespread and gradated. By exculpating parents (i.e., exonerating them from having caused their children's condition), geneticization made autism a far more desirable diagnosis and enabled the enormous levels of autism parents' advocacy that followed (King 2008; Silverman 2011). The year after Rimland's book was published, he founded the National Society for Autistic Children (NSAC). As the society became more assertive and formed ties to therapists and researchers, the number of parents affiliated with it began to increase (Eyal et al. 2010, pp. 167–93). Thus, the geneticization of autism was invested, from the very start, with the interest of autism parents in destigmatization.

An explanation in terms of destigmatization, however, is limited. The turn to geneticization cannot be understood simply as a function of what it disabled—namely, the stigma of having caused your child's autism—but more important in terms of what it enabled: a rearrangement and inten-

sification of the bond holding the autistic dyad of parent-child together and therefore the creation of a distinctive form of "biosociality" (Rabinow 1992). It is striking that even as Rimland argued forcefully against the psychogenic explanation, he repeatedly endorsed the main piece of evidence on which it relied, namely, that the parents were similar to their children; that they were cold, highly intellectual, prone to abstract occupations, and lacking an interest in people (Rimland 1964, p. 160). But if his interest was mainly in destigmatization, why would he stray so dangerously close to what was considered the most damning evidence against the parents? The answer is that geneticization did not decouple the Kanner's dyad but served to rearrange the relations within it and to forge an even stronger tie linking parent and child.

First, the similarity between parents and children, together with his insistence on the rarity of the disorder, enabled Rimland to argue that autistic children were not retarded.[8] "Autistic children," he said, "were to have been endowed with unusually high intelligence" (Rimland 1964, p. 124). This was the meaning of their similarity to their intellectual and cold parents. They had inherited a potential that had somehow gone awry (p. 127). No wonder that NSAC was, for most of its existence, an organization of middle-class parents and that autism was considered for many years to be a disorder characteristic of upper-middle-class families (Schopler, Andrews, and Strupp 1979; Wing 1980). Only upper-middle-class parents had the resources and knowledge to combat the stigma attached to them, and only the link to middle-class status represented by the similarity between parents and children protected the latter from the stigma of retardation. Second, as Silverman (2011, pp. 142–43) perceptively noted, "genetics provides an effective vocabulary for expressing responsibilities and experiences of membership that develop out of love, friendship and loyalty." For parents to understand themselves as similar to their children because of a common genetic endowment and a common neurological difference entailed the possibility of forging an emotional bond with a child who, previously, was described as "alien." This was even truer for fathers, who often would be initially noncooperative (p. 141).

Third, the notion that the parents are similar to their children because of a common genetic basis also legitimates the parents' claim to be "experts on their own children" and to speak for them not only as caregivers but also from the perspective of sharing certain autistic characteristics and having an intimate understanding of autistic experience from within. Put differently, genetic vocabulary creates a discursive position from which one is

[8] This was crucial. If Rimland merely destroyed the psychogenic explanation, and left autism as a fairly common disorder caused by genetic and brain mechanisms, it would have become indistinguishable from MR. He would simply have transferred the stigma from the parents to the children.

able to speak for, represent, and thereby bring into being and knit together autism as a distinctive biosocial formation (Silverman 2011, pp. 142–43).

This is how geneticization figured in autism's early looping processes. Not genetics per se, but the genetic interpretation of the similarity between parents and children. As Silverman (2011, p. 143) put it, geneticization served as a vehicle to form "certain kinds of kinship relations . . . as well as expressions of commitment and obligation," not only by "recognizing similarities between parents and children with autism" but also by "seeing a relationship of likeness between 'high' and 'low' functioning autistic individuals." Contrary to Rimland's intentions, the geneticization of autism therefore contributed to its quantitative expansion and pointed toward reformulating it as a spectrum.

Loop 3: The Discovery of a Broader Phenotype

While the geneticization of autism began with the parents, it was solidified as a fact through biomedical research. In 1977, Folstein and Rutter published the results of a study comparing MZ and DZ twin concordance for autism, demonstrating that it was highly heritable (1977*b*). Their study was hailed as a breakthrough, and a summary version appeared in *Nature* (Folstein and Rutter 1977*a*). It is still remembered by researchers, parents, and activists as "one of the most significant studies in the history of autism" (Feinstein 2010, pp. 147–48).

There is one cavernous wrinkle in this story, however: what Folstein and Rutter actually found was an estimated autism heritability of 36%—significant evidence of genetic determination but much lower than subsequent estimates of 80%–90% based on similar data and methods. It was a secondary finding that put the MZ concordance of a "broader linguistic or cognitive impairment" or simply "cognitive disorder (including autism)" at 82% (Folstein and Rutter 1977*b*, pp. 302, 310; 1977*a*, p. 727). "What is inherited," they said, "is a form of cognitive abnormality which includes but is not restricted to autism" (Folstein and Rutter 1977*b*, p. 310). To be more specific, five of the seven MZ twin pairs not concordant for autism had a diagnosis either of MR or of language/speech disorder.[9]

To be blunt, what Folstein and Rutter found in 1977 was quite ambiguous. One could interpret it as indicating that autism was only partly heritable or that the distinction between autism and MR was problematic. However, this is not how the finding was interpreted. As Rutter (2000) put it in retrospect: "The replicated evidence from both twin and family studies undertaken in the 1970s and 1980s indicated both *strong genetic influences and the likelihood that they applied to a phenotype that was much broader*

[9] And four of the 11 pairs were concordant for MR, i.e., the same as for autism.

than the traditional diagnostic category of autism. . . . This implied that *genetic liability extended beyond 'autism proper.' It also raised questions about the diagnostic boundaries of autism and led to an appreciation of the need to consider the likelihood of a broader phenotype of autism*" (pp. 3–4; our emphasis). Clearly, Folstein and Rutter interpreted their results as evidence that autism was a spectrum disorder and that diagnostic criteria needed to be revised accordingly (see also Folstein 1996), even though only one of the six children with an autistic twin who were concordant for this broader "cognitive or social impairment" actually "had social or behavioral problems *at all reminiscent of autism*" (Folstein and Rutter 1977*b*, p. 303; our emphasis). Despite a liberal interpretation of what that meant (they counted shyness, dog phobia, and a "psychiatric disorder of uncertain nature"), their efforts were inconclusive (Folstein and Rutter 1977*b*, pp. 303–4; Bailey et al. 1995, p. 63).

Their finding became stronger, however, over the following decades, which witnessed a concerted effort to change autism's diagnostic criteria to capture a "broader phenotype." In quick succession, NSAC (Ritvo and Freeman 1977), Wing and Gould (1979), Schopler et al. (1980), and Rutter himself (1978) each published their own, roughly similar, spectrum-type diagnostic criteria emphasizing a trio of communicative, social, and behavioral impairments. Significantly, all four versions were formulated in close coordination with either the British or the American parents' associations, and all the main actors sat on the DSM-III-R committee rewriting autism's diagnostic criteria, which essentially adopted Wing's version (Waterhouse et al. 1992).[10] The finding that a broader phenotype was far more heritable therefore served as evidence in support of diagnostic expansion.

In the years since, the observed heritability of autism increased further still. A 1995 study by Bailey et al., for which Rutter was the last author, sought to replicate Folstein and Rutter's 1977 findings combining 19 twin pairs from the original study with 28 new ones. Bailey et al. found a 60% MZ concordance rate for autism proper (69% in the new sample) versus 0% DZ concordance and 92% MZ versus 10% DZ concordance for a "broader spectrum of related cognitive or social abnormalities." They defined autism using the International Statistical Classification of Diseases and Related Health Problems, 10th edition, criteria (Bailey et al. 1995, p. 66), which were similar to the broader criteria introduced in DSM-III-R. Because they were using a sample that significantly overlapped with the older study, this strongly suggests that the observed heritability of autism changed because its diagnostic criteria were revised in accordance with mounting evidence

[10] DSM-III-R refers to the *Diagnostic and Statistical Manual of Mental Disorders*, vol. 3, rev., published by the American Psychiatric Association. Throughout, we reference five different iterations of this handbook: DSM-III (1980), DSM-III-R (1987), DSM-IV (1994), DSM-IV-TR (2000) and DSM-V (2013).

for the heritability of a "broader autism phenotype" (e.g., Bailey et al. 1995; LeCouteur et al. 1996; Piven et al. 1997; Pickles et al. 2000). As mentioned earlier, a recent twin study by Nordenbæk et al. (2013) using even more inclusive diagnostic protocols estimated ASD heritability to be approximately 95%. While the introduction of larger sample sizes and more sophisticated heritability estimation techniques has led to the publication of considerably lower heritability estimates in recent years (see above; see also Colvert et al. [2015] for a recent such study and a review of the literature), as we noted earlier (see n. 4), there is evidence that these lower estimates also increased over time (Liu et al. 2010). Regardless, throughout the period of the third loop discussed here, autism heritability was estimated only through small-*n* twin studies. It is not hard to see how broadened diagnostic criteria would increase heritability estimates obtained in this way and therefore serve to reinforce the perceived validity of this broader concept of autism.

Thus, the movement begun with Rimland's geneticization—which relied on autism being rare and without gradations—looped in interaction with genetic evidence to render autism a broad spectrum. In sum, the turn to understand autism as a strongly genetic condition both enabled and required significant diagnostic expansion: it did not just change how we understand ASD etiology; it helped change the category of autism itself.

Loop 4: Increased Genetic Heterogeneity

Let us summarize the argument thus far: Kanner's naming of autism brought a dyadic human kind into being—the autistic child and autism parent. This first loop created the conditions for a second that saw autism parents seek to modify the meaning of their similarity to their children from one of psychogenic causation to genetic correlation. Geneticization not only destigmatized autism but also enabled parents to see themselves as similar to their children and to reconfigure autism from a narrowly delineated disorder to a gradated one up to and including the "near normal." This set in motion the third loop of autism genetics because it allowed researchers to interpret the finding that a "broader phenotype" was more heritable as saying something significant about the nature and scope of autism. Yet, as we hinted above, this was no simple "discovery." After all, in Folstein and Rutter's seminal 1977 study the heritability of autism proper was not high. Moreover, most of their evidence for a broader phenotype consisted of concordance with MR, not with the near normal type (see table 2 in Folstein and Rutter 1977*b*). Nevertheless, diagnostic expansion encompassing both high- and low-functioning people with "autistic traits" was the direction in which Folstein, Rutter, and their allies sought to interpret the significance of their results. In short, each loop was set in motion by its predecessor, but

each expanded the delineation of autism in different directions and with novel consequences. Likewise, the third loop precipitated a fourth that is still in motion: the diagnostic expansion of autism that was so bolstered by Folstein and Rutter's results looped to produce its enormous genetic heterogeneity. This is the key empirical claim of this article.

While Folstein and Rutter (1977*b*, p. 309) were agnostic about the mode of inheritance—apart from excluding simple Mendelian inheritance—they still hoped to show that autism is determined by a small number of genes (Bailey et al. 1995, p. 73). However, the evidence has consistently pointed in the other direction: autism, like many other conditions in our postgenomic age, is extremely genetically heterogeneous. A recent review of the genetic abnormalities associated with autism noted that no less than 124 gene mutations and 55 chromosomal anomalies have been associated with autism spectrum disorders, almost all of them rare anomalies also associated with ID (Pinto et al. 2014; see also Laumonnier et al. 2004; Abrahams and Geschwind 2008, pp. 352–53; Marshall et al. 2008; Betancur 2011).

We argue that there were two sources of increased heterogeneity, both traceable to a process of looping. First, there was undoubtedly an increase in *observed* heterogeneity due to technological innovation and intensified scrutiny of the autism population by geneticists: by examining more and more people with autism using increasingly advanced genetic testing techniques, researchers identified and reported a host of mutations that are associated with autism. It is impossible to know how many of these mutations were present in the populations diagnosable with autism as described by Kanner, DSM-III, and other decades-old diagnostic criteria for autism. The second and more contentious claim is that shifts in diagnostic practice have brought a raft of previously unrelated mutations into the autism population, transforming its *actual* genetic heterogeneity: as the population diagnosable with ASDs grew in size and phenotypic range, mutations that could not have been meaningfully associated with autism 20, 30, or 40 years ago—even with today's genomic testing technologies—came to be strongly associated with it. In what follows, we provide evidence for this claim based on those mutations that have been observable for decades and an explanation that, based on a looping mechanism, allows one to understand both processes—increases in observed and actual genetic heterogeneity—as taking place in tandem and reinforcing one another.

The increased scrutiny of autism by geneticists is evident in figure 1. From only a handful of papers referring to both autism and genetics in their titles during the 1980s, there are now well over 100 such papers published annually.[11] While retrospective histories of the field trace the interest in autism

[11] Our Web of Science search string was "TI = (autis* AND (gene OR genes OR genetic* OR DNA OR GENOM* OR CHROMOSOM* OR heritab* OR mutation*))."

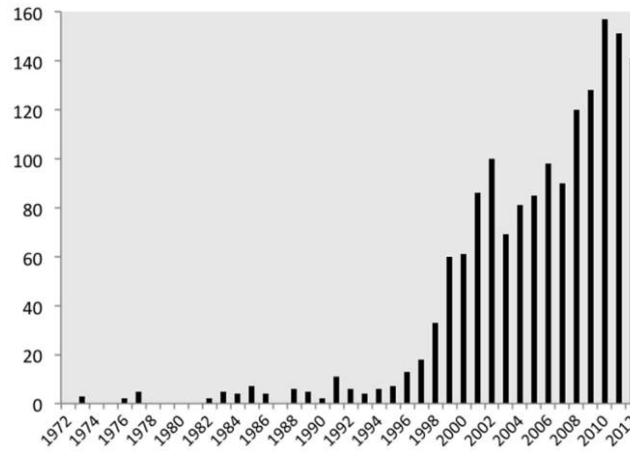

FIG. 1.—Papers published per year with autism and genetics terms in their titles

genetics to Folstein and Rutter's (1977*a*, 1977*b*) foundational study—by far the most widely cited paper in our sample published before the 1990s—it is instructive that the exponential increase in the number of publications dates not from 1977 but from 1997. Indeed, the most cited work on autism genetics is a paper that predated this increase by only two years. It replicated Folstein and Rutter's study using newer diagnostic criteria and found higher heritability (Bailey et al. 1995).

Two things happened in 1997 to help generate the takeoff in autism genetics. First, in response to increased biomedical and political interest in autism, National Institutes of Health (NIH) funding for autism research began to increase rapidly, from $22 million in 1997 to $108 million in 2006, when the Combating Autism Act mandated a further increase of NIH funding to $210 million by 2011.[12] Of all the fields funded by the NIH's autism budget, genetics has grown the fastest (Singh et al. 2009). Second, 1997 also witnessed the formation of the Autism Genetic Resource Exchange (AGRE) and the Autism Genetics Cooperative (AGC), the first being the most widely used gene repository pooling together samples from over 12,000 families, the second being a framework of cooperation and pooling of samples among the top researchers in the field (Singh 2010; Silverman 2011, pp. 155–60;

Restricting the analysis to titles undoubtedly misses much of the field, but given the change in Web of Science capture for topic terms in 1991 onward, it is the only reliable metric.

[12] Much of this increase came during a period of expanding total NIH budgets. However, the steep rise in NIH spending on autism research has continued even amid the stagnating overall NIH budgets of recent years. For data on NIH annual budgets, see http://officeofbudget.od.nih.gov/spending_hist.html.

Tabor and Lappé 2011). Crucially, these developments were all initiated and driven by parental activism.[13] Increased NIH funding was in large part the product of intense lobbying by autism parents' organizations (see Epstein [1996] and Best [2012] on the way that advocates shape funding for medical research). They appealed directly to Congress and in 2000 gained the creation of the Interagency Autism Coordinating Committee through which parent representatives and a "parent advisory committee" interact directly with the leaders of NIH and the Centers for Disease Control and Prevention (CDC; Bagnall 2015). Autism parents' organizations also began raising their own funds for genetic research (Singh et al. 2009). By the same token, AGRE and AGC were created by parents' organizations—Cure Autism Now and the National Alliance for Autism Research, respectively—that used their moral capital as well as their control of material samples to force researchers to cooperate and share samples and results. Their explicit aim was to speed up the rate at which results were obtained and published, and they were spectacularly successful in this regard (Silverman 2011, pp. 155–59). The bottom line is that the increase in observed genetic heterogeneity of autism was not merely the result of improved technology or scientific interest but also strongly driven by the work of parents' organizations whose investment in the geneticization of autism was intertwined with the spirals of looping discussed above.

We argue, moreover, that looping also served to increase the actual genetic heterogeneity of autism: by effecting diagnostic change, looping broadened the population captured by the autism diagnosis in such a way so as to increase the number of genetic anomalies that have significant associations with ASDs. The relevant counterfactual is that, if autism had remained the thing that Kanner diagnosed—a disorder that was mutually exclusive with MR and that was defined by "cardinal symptoms" necessary for diagnosis—this growth in autism's genetic heterogeneity would have been impossible. Recall that all of the new mutations are also linked to MR. If a concurrent diagnosis of autism with MR was not meaningful—as both Kanner (1949) and Rimland (1964, pp. 10–11, 139, 160), for example, argued—it would have been impossible to link many of these mutations with autism. Moreover, even as the DSM-III (1980) permitted a concurrent diagnosis of autism with MR, it still required, in deference to Kanner's description, that children

[13] Of course, other related factors were important as well: autism heritability findings supported the focus on genetics; genetics research more generally was growing quickly, with technological innovation serving as an important driver (Ledbetter 2008); and epidemiological evidence that autism prevalence was growing, and the rhetoric of "epidemic," also provided a powerful rationale for conducting research on the genetics of autism. Conversely, the parents' movement is anything but monolithic, and activists pursued many other lines of research on the causes of autism—from environmental toxins to the notorious (and spurious) association with the MMR (measles, mumps, and rubella) vaccine.

could not qualify for the diagnosis of autistic disorder if they did not show "pervasive lack of responsiveness to other people (autism)" (DSM-III, p. 90). It would have been impossible to identify 179 genetic mutations associated with both ID and ASDs (Pinto et al. 2014; see above), let alone accommodate them all within a single framework, if one were still working with Kanner's or DSM-III's conception of autism. The expanded diagnostic criteria introduced by DSM-III-R and DSM-IV, as well as the creation of intermediary categories like "pervasive developmental disorder (not otherwise specified)" (PDD-NOS) and "atypical autism," was the bridge that made strong associations between genetic disorders and autism viable. As a result, the autism population expanded to accommodate a growing number of people bearing genetic mutations.

Increased scrutiny and technological innovation are therefore only part of the story: when "autism" looped into the broad spectrum disorder that it is today, it absorbed new, previously unrelated genetic mutations into its population. Some of these mutations, which are most often de novo, may have themselves become somewhat more prevalent due to increased parental age (Liu et al. 2010) as well as increased use of artificial reproduction technologies and improved neonatal care increasing survival rates among children with congenital anomalies. Still, the crucial point is that these mutations would not have increased the actual genetic heterogeneity of autism if diagnostic change had not brought their bearers into the autism population. The looping argument therefore identifies a mechanism that can help explain autism's current genetic heterogeneity. In the next two sections, we explain how this mechanism came into effect and provide qualitative and quantitative evidence supporting this argument.

FRAGILE X AND THE CONDITIONS OF AUTISM'S GENETIC HETEROGENEITY

If looping increased the actual genetic heterogeneity of autism, it should be observable as a change over time in the ASD rates of people with genomically designated conditions. The obvious place to begin is with fragile X syndrome (FXS), the first genomically designated disorder to be strongly associated with autism. By examining how the association between ASDs and fragile X was first formed, moreover, we are able to outline the broader changes that created the conditions of possibility for understanding autism as a genetically heterogeneous condition.

Although X-linked MR had been identified on the basis of family pedigrees from 1943 on (Martin and Bell 1943), it was only in 1969 that the discovery of a "fragile site" on the X chromosome allowed researchers and clinicians to identify a molecularly specific subtype characterized by varying degrees of developmental delay, macroorchidism, and mild facial dys-

morphism that eventually came to be known as fragile X syndrome (Lubs 1969). In 1991, the fragile X mutation was specified as a 200+ CGG copy-repeat on the FMR1 gene (Verkerk et al. 1991), and the syndrome has been delineated and diagnosed on that basis ever since.[14]

From 1969 through the early 1980s, there was no mention in the literature of an association between fragile X and autism (before 1969, as a form of X-linked MR, fragile X was by definition mutually exclusive with an autism diagnosis). A few case studies of single individuals with fragile X who were diagnosed with autism were reported in the early 1980s (e.g., Brown et al. 1982*a*, 1982*b*; Gillberg 1983; Watson et al. 1984). The first study to claim that there was a high autism rate in the fragile X population was the product of collaboration between Randi Hagerman (a developmental pediatrician who cofounded the first fragile X advocacy organization in 1984) and Bernard Rimland (the aforementioned autism parent/researcher/activist; Levitas et al. 1983; Hagerman et al. 1986). In 1986, they published the results of a study examining 50 males with fragile X for autism and autistic traits. They reported that "sixteen percent of patients fulfilled all of the DSM III criteria for Infantile Autism and an additional 30% fulfilled criteria for Infantile Autism Residual State. Thirty-one percent of patients had autism using the ABC checklist but none of the patients fit the classical Kanner syndrome." They also claimed that "some autistic traits were seen in almost all of the 50 fra(X) patients" (Hagerman et al. 1986, abstract). While the finding that the fragile X mutation frequently caused autism were strongly disputed at least until the mid-1990s (see below), recent studies find that around 30% of males with FXS have autism, while 60% could be diagnosed with ASD. FXS is currently considered "the most common known single gene cause of autism"; conversely, "Autism is a common problem in those with FXS" (McLennan et al. 2011, pp. 216, 220). An even more recent study evaluating 182 FXS cases put ASD and autism rates at 83.6% and 48.6%, respectively (Moss et al. 2013), although estimates vary considerably and there is emerging evidence that DSM-V's criteria will lower the proportion of FXS patients diagnosable with an ASD (Wheeler et al. 2014).

To reiterate our initial point: as the rates of autism/ASD in FXS patients increased over the last 30 years from 0% to approximately 60% and upward of 83.6%, the genetic heterogeneity of autism increased correspondingly. This did not happen automatically or straightforwardly: the initial evidence linking fragile X and autism, like the early heritability studies on autism before it, produced ambiguous, contested results that can only in hindsight

[14] It should be noted that, before the dissemination of that test, a variety of cytogenetic techniques were used to identify the "fragile site" at Xq27.3. These techniques would often deliver a high volume of what would now be considered false positives, making it somewhat difficult to compare rates of fragile X before and after 1991.

be seen as having established a relatively certain biomedical fact. Moreover, this brief history of the fragile X–autism link immediately underscores the point that the strength of the association between the two depended on the diagnostic criteria used for the latter: the proximate cause for the increase is clearly diagnostic change. Despite intense scrutiny, the 1986 study could not produce even one child who fit the classical Kanner syndrome. This explains why nobody diagnosed autism in fragile X patients before DSM-III (1980). It constitutes powerful, if preliminary, evidence supporting our counterfactual above: Kanner's "autism" could not have become such a genetically heterogeneous condition even if it had been as closely observed as autism is today using the same genetic testing techniques. The 1986 study also showed that when somewhat broader diagnostic criteria are used (for "autism residual state" or the ABC [Autism Behavior Checklist] criteria), the rate of autism in FXS increases further still. Indeed, the current studies demonstrating much higher rates of FXS in autism or ASD use the broader criteria introduced in DSM-III-R (1987), DSM-IV (1994), and other diagnostic tools.

We can gain insight into the processes that made the autism-FXS association possible by asking which diagnostic changes contributed most to forging and strengthening it and then tracing the conditions that underlay those changes. The first and most obvious point is that it would have been impossible to diagnose autism in a form of X-linked MR before DSM-III formally permitted a concurrent diagnosis of autism and MR. Second, the ability to observe isolated "autistic traits" in otherwise nonautistic FXS patients depends on the type of changes introduced by DSM-III-R (1987) and DSM-IV (1994), which broke down the unity of Kanner's cardinal symptoms into separate scales of variable impairments in language, communication, and repetitive behaviors. The more it became possible to diagnose autism by the presence of relatively independent traits of variable severity, with social and communicative impairments replacing Kanner's "profound aloneness," the more fragile X probands could be given the ASD diagnoses (see Reiss and Freund [1990] on DSM-III-R autism diagnosis and FXS).

These changes in diagnostic criteria, however, are themselves merely the surface manifestations of the transformation that enabled the association between autism and fragile X. Even before DSM-III, for example, there were researchers who claimed that children with autism were comorbid for MR in up to 94% of cases (e.g., DeMyer et al. 1974; Kraijer 1997, pp. 30–42; see also Feinstein 2010, pp. 145–46). Conversely, even after DSM-III permitted a concurrent diagnosis of autism and MR, the association between autism and fragile X was hotly contested by researchers who either rejected the idea that autism and MR could be comorbid or argued that the rates of autistic traits in FXS probands were not significantly higher than

in IQ-matched controls (e.g., Einfeld, Molony, and Hall 1989; see Cohen et al. [1991] for a review of this debate). We will see how a similar obstacle had to be overcome around 20 years later regarding autism and Phelan-McDermid/22q13.3 deletion syndrome. As late as 1994, Rutter dismissed the association between autism and fragile X as "quite low." He argued, citing Hagerman herself, "that *some* autistic features were indeed quite common but the overall clinical picture was rather different" (Rutter et al. 1994, 316).[15]

We are not interested in adjudicating who was wrong and who was right in this matter. Nor do we mention the controversy in order to cast doubt on the validity of either Hagerman et al.'s (1986) findings or more recent findings of even higher rates of ASDs in FXS patients. Rather, we want to explain the conditions and historical processes that made it possible for Hagerman and Rimland to formulate a new statement about the association between autism and FXS that was not possible to formulate earlier. What conditions allowed this statement to be formulated, repeated, put into wider circulation, and ultimately become stronger over time? This is not a question of the intrinsic truth of the statement or its correspondence to reality. Rather, it is ultimately a question of the network of actors, devices, concepts, and institutional, discursive, and spatial arrangements that give the statement the value of truth—that make it thinkable, defensible, and actionable (Foucault 1977, 2002; Callon 1986; Latour 1987; for a recent sociological adaptation, see Eyal 2013). We mention the controversy in order to demonstrate that changes in the DSM, by themselves, were not sufficient to formulate and stabilize the statement that it was valid to give comorbid autism and MR diagnoses. By tracing the "surfaces of emergence" (Foucault 2002, p. 41) for this statement, we can show that there were distinct institutional, discursive, and social conditions of possibility for the association between autism and fragile X, and by extension for the associations between autism and the many other genomically designated conditions that have further increased autism's genetic heterogeneity.

Institutional Conditions of Possibility

Rimland, we saw, rejected the possibility that autism and MR could be comorbid in 1964. Had he changed his mind by 1986? Not exactly. Rather, the

[15] Elsewhere, Rutter and Bailey called the strength of the fragile X–autism correlation into question, on the grounds that they were distinct "behavioural phenotypes" (Bailey et al. 1993, p. 676) and that stricter diagnostic criteria for autism (p. 682), as well as more stringent cytogenetic techniques (p. 683), weakened the association considerably; they even excluded from their follow-up study an MZ twin pair who had been part of Folstein and Rutter's sample, on the grounds that they had since been diagnosed with fragile X (Bailey et al. 1995, p. 67).

discursive conditions had changed such that the very same statement—"autism and MR can be comorbid"—had a different meaning in 1986 than it did in 1964. Rimland could therefore assent to it without modifying his original commitments. Studies presenting evidence that MR and autism were comorbid began to appear in the early 1970s (e.g., DeMyer et al. 1974), yet the response of many parents, activists, and researchers at the time—and still today—was to doubt the validity of administering IQ tests to children with autism (Kraijer 1997, pp. 40–42). Lorna Wing, a preeminent autism expert, mother of an autistic girl, and a cofounder of the British parents' association, argued that children with autism performed poorly on IQ tests not because they were retarded but because of "sensory and language handicaps" that interfered with their performance (Wing 1973, p. 112). Speaking to the annual conference of the American autism parents' association, she went on (p. 113) to cast doubt on the very "idea that mental retardation exists as a unitary condition." Autism researchers, therapists, activists, and parents essentially rejected the notion that IQ measured intelligence as a generalized aptitude. They argued that the true capabilities of children with autism could only be assessed by attending to their "splinter skills" and "islets of ability"; by measuring, for example, only "performance IQ" and ignoring verbal IQ results; and by administering intensive therapy and employing assistive technologies to overcome their uneven cognitive profile (Kraijer 1997, pp. 23, 37–42).

This deconstruction of MR was built into the concept of autism from its very beginning, ever since Kanner (1949, pp. 11, 27–28) referred to it as "apparent feeblemindedness." However, it remained speculative and carried little meaning within the institutional matrix of Kanner's time, which consigned most feebleminded children to large residential institutions where careful differential diagnosis and treatment were impossible. In the wake of the deinstitutionalization of MR, however, Wing's argument became part of the project of building a new institutional matrix composed of early intervention, special education, and community treatment on a "noncategorical" basis (Eyal et al. 2010, pp. 190–91). Within this matrix, it became possible to treat autism and MR as comorbid because the institutional underpinnings of the category of MR "as a unitary condition" had weakened, allowing Rimland to assent to the statement that MR was frequently comorbid with autism without abandoning the potential for development. To put it simply, Rimland could help forge the FXS-autism link in 1986 because he could construe it as indicating that autism is the correct diagnosis, FXS is one of its causes, and MR is merely a label that indexed an IQ score below 70 and adaptive deficits rather than a diagnosis in its own right.

At the same time, however, Hagerman probably construed the FXS-autism findings quite differently. Like many fragile X researchers and ad-

vocates today, she most likely thought of FXS as the fundamental diagnosis and both autistic behaviors and MR as common-but-variable elements of its behavioral phenotype (Hagerman and Jackson 1985; Brown et al. 1986, pp. 344–45; Reiss, Feinstein, and Rosenbaum 1986; Reiss and Freund 1990; Gillberg 1992). Attending a fragile X conference today, parents and researchers alike discuss the way that many children with fragile X display repetitive behaviors and language/communication deficits (i.e., autistic traits), even as they exhibit strong social impulses and awareness that stand in sharp contrast to classic autism.[16] In this way, fragile X researchers and advocates can at once embrace the crucial behavioral overlaps with autism, the therapies and services an ASD diagnosis can afford families, and the intense interest of autism researchers, even as they qualify the nature of that association and point to profound differences in FXS's behavioral and cognitive phenotype.

Discursive Conditions of Possibility

How could Rimland and Hagerman—not to mention autism parents, advocates, and researchers and their counterparts dedicated to FXS—collaborate even as they held seemingly incongruent understandings of the autism-FXS link they were creating? This question points to another element of the conditions of possibility for the FXS-autism link. A series of conceptual and technical developments in the field of genetics, which one begins to see deployed in the FXS literature soon after its molecular basis was discovered in 1991, led researchers to begin studying genetic disorders like FXS in order to elucidate the biological pathways that lead to common neuropsychiatric conditions (see Baumgardner, Green, and Reiss [1994] for a review that places special emphasis of FXS). This line of study has become increasingly prevalent in FXS research over the last couple of decades (e.g., Hagerman 1997; Feinstein and Reiss 1998; Kaufmann et al. 2004; Belmonte and Bourgeron 2006; Moss and Howlin 2009; Hagerman, Hoem, and Hagerman 2010; Budimirovic and Kaufmann 2011; Krueger and Bear 2011). In this new framework, the potential clash embedded in the autism-FXS link—is it really autism or is it really FXS?—is dissolved

[16] As Hagerman herself put it in a question-and-answer session at the most recent meeting in 2014, people with fragile X do exhibit classic autistic traits like an aversion to certain forms of social interaction as well as eye contact. However, in fragile X an aversion to parties or meeting another person's gaze is caused by anxiety and overstimulation resulting from an acute awareness of others, not the detachment and absence of a "theory of mind" that characterizes classic autism. See the National Fragile X Foundation's page "FXS and Autism: Similar but Different" for a similar account: http://www.fragilex.org/fragile-x-associated-disorders/fragile-x-syndrome/autism-and-fragile-x-syndrome/fxs-and-autism-similar-but-different/.

as each disorder is situated within distinct, potentially complementary disease ontologies.

Instead, the new approach allowed the two sides to collaborate by reformulating the object of genetic research as an increasingly complex set of molecular pathways linking mutations, DNA regulators, RNA transcription, upstream and downstream effects, protein production, neural/brain mechanisms, phenotypic outcomes, and ultimately psychiatric diagnoses. In short, when "pathways" became a key object of genetics research (Jacob 1993, pp. 265–66; Rheinberger 2010, pp. 159–69; Müller-Wille and Rheinberger 2012), FXS could begin to serve as a "genetic model" for autism. Conversely, autism could be situated at the end of a "final common pathway" for multiple genetic abnormalities, like the FMR1 mutation, that converge on a shared physiological mechanism and a common behavioral phenotype (see Reiss et al. [1986, pp. 725–29] for an early articulation of this framework). Furthermore, as autism has become a set of deficits in several partly interdependent domains, its constituent elements could be parsed out into what are now called "endophenotypes" that can be more powerfully correlated with genetic variants (Gottesman and Gould 2003; Abrahams and Geschwind 2008; Betancur 2011; Waterhouse 2013, pp. 77–91). In this way, researchers can recognize important differences between the FXS phenotype and classic autism without jeopardizing the value of the connection between them. This new "discursive formation" (Foucault 2002) in psychiatric genetics made it possible to identify important behavioral commonalities between FXS and autism and mobilize the former as a genetic model for the latter and yet at the same time point to profound differences between the two and maintain fragile X's status as a distinct, biologically grounded disorder.

As we have argued elsewhere, the idea of the "final common pathway" helps autism genetics function as what Galison (1997) has described as a "trading zone"—a framework for cooperation and exchange between different communities of scientists despite potentially conflicting goals and understandings of the objects being exchanged (Navon and Eyal 2014). Focusing on the intermediate processes that lead from a genetic mutation to an autism diagnosis allows ASD researchers, parents, and advocates, on the one hand, and their counterparts dedicated to rare genetic disorders (represented first and foremost by FXS), on the other, to cooperate on the shared goal of finding treatments or even a cure (see below) while suspending potential disagreements about ontologies and languages.

Social Conditions of Possibility

As Galison emphasizes, the exchanges taking place in a trading zone not only benefit individual traders but ultimately create enduring ties and com-

mon interests between the two communities involved in the trade. Similarly, the association between autism and fragile X was also a link between two biosocial communities, each consisting of patients, parents, advocates, and researchers, and the developing ties between them served to further strengthen the association between autism and fragile X. The two coauthors of the 1986 study were each leading figures not only in research but also in advocacy: Rimland not only cofounded NSAC but also headed the Autism Research Institute, the outlet of which—*Autism Research Review International*—reported fragile X–related findings enthusiastically to its readership of parents and allied researchers (1987, 1989, 1991); Randi Hagerman, similarly, was cofounder of the National Fragile X Foundation and served on its board for 25 years.[17] The National Fragile X Foundation is a parent-led organization that is looked to by other advocacy organizations for rare genetic disorders as perhaps the exemplary model for success (Navon 2013). The research program Hagerman and Rimland inaugurated not only linked the fragile X mutation to autism but also created an enduring link between fragile X parents, advocates, and researchers, on the one hand, and autism parents, advocates, and researchers, on the other, translating and aligning the interests of these two biosocial communities. It gave fragile X families access to a host of behavioral and language therapies developed for children with ASDs, and it gave the autism community the promise of a biological model that could one day lead to drug development. Crucially, they were able to draw on the common "pathway" framework to combine efforts in lobbying for increased funding for genetics research (Navon and Eyal 2014).

With the support of autism organizations, fragile X advocates have secured millions in research funding through the U.S. Department of Defense, the CDC, and the NIH. The NIH now designates FXS a priority topic with some $36–$37 million per year allocated for 2014–16 as part of a steady upward trajectory over the last several years.[18] Throughout, the capacity of fragile X to serve as a biological model or "portal" for understanding and developing treatments for ASDs has been an important driver of this extraordinary level of interest and investment (e.g., Trans-NIH Fragile X Research Coordinating Group and Scientific Working Groups 2008, pp. 4–8). The leading center for fragile X research and treatment, University of California, Davis's MIND Institute, was established with funds from three "founding families" whose goal was and is to find a cure for autism. Indeed fragile X work has been hailed as the first instance of "fulfilling the promise of molecular medicine" (Krueger and Bear 2011, p. 411) as knowledge

[17] See the National Fragile X Foundation website at http://www.fragilex.org/.

[18] See NIH's "Estimates of Funding for Various Research, Condition, and Disease Categories": http://report.nih.gov/categorical_spending.aspx.

about the FMR1 mutation has led to the development of animal models, to the investigation of gene-protein-physiological pathways, and, despite recent setbacks, to the development of several pharmaceutical compounds and clinical trials (Harris 2010; Pollack 2013). None of this would have been possible if fragile X had remained simply a form of X-linked MR.

AUTISM AND GENOMICALLY DESIGNATED CONDITIONS

As discussed in the introduction, we use the published literature on ASD rates in genetic disorders as a strategic research site to show that a looping mechanism involving diagnostic change transformed the genetic makeup of the population captured by the autism diagnosis. By restricting our analysis to cases of genomic designation—conditions delineated and diagnosed strictly on the basis of genetic mutations—we are able to show how the very same rare, highly penetrant variants that were not associated with autism before the fourth loop discussed above have, in recent years, become powerfully linked to it. Indeed, some of these genomically designated conditions are now being leveraged as biological models for autism research.

We begin by presenting some descriptive statistics on the development, over time, of research on the relation between autism and the chromosomal disorders referenced in Betancur's (2011) authoritative list of mutations associated with ASDs. We follow these with a table comparing snapshot histories of ASD rates in 13 genomically designated conditions with a long enough history (at least 15 years since the relevant mutation was discovered) to capture meaningful trends. Finally, we provide a qualitative analysis of three strategically selected cases out of these 13: Williams syndrome, Phelan-McDermid syndrome, and XYY syndrome. As we will see, the same institutional, discursive, and social factors that made the association between fragile X and autism possible and strong were also central to the processes that increased the rates of autism in these three genomically designated conditions.

Development of the Field

Figure 2 reports keyword rates in a population of papers generated by a Web of Science search string.[19] The search string seeks to capture all the papers about the association between autism and topics related to the genomically designated chromosomal disorders listed by Betancur (2011).[20] The total number of original research articles captured by the search string appears

[19] Our approach to collecting this population of papers is explained in the appendix.

[20] For a complete explanation of which genetic disorders are included in our analyses, see the appendix.

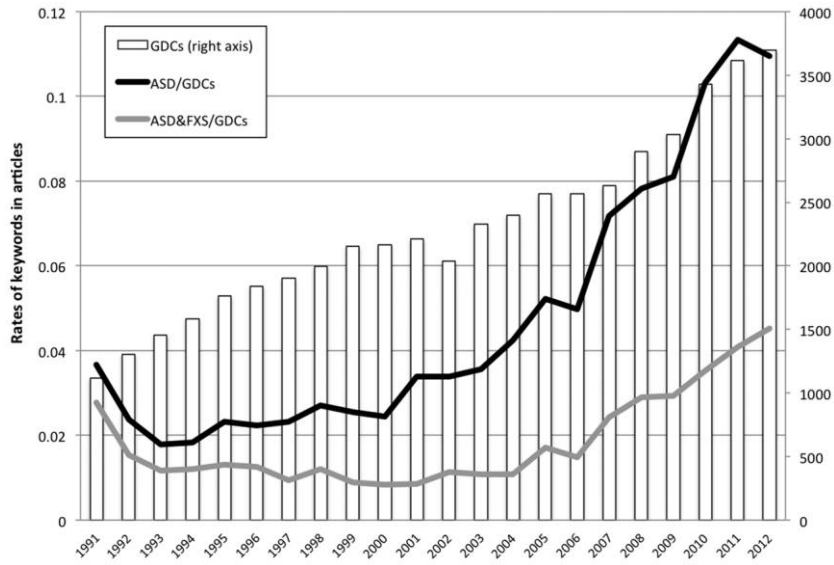

FIG. 2.—Papers with keywords related to genomically designated conditions and the subset with autism and fragile X keywords by year, 1991–2012.

as bars (right-hand *y*-axis). The proportions therein with keywords related to autism on the one hand and autism and fragile X on the other appear as black and gray lines, respectively (left-hand axis).

Figure 2 tells a fairly straightforward story. First, the literature as a whole has more than tripled over the last two decades, from 1,119 papers in 1991 to 3,699 in 2012. Second, the proportion that pertains to autism increased rapidly, especially after 2000, reaching a peak of around 11.34% in 2011. In absolute terms, there was an average of 41.5 articles related to autism annually in the decade 1991–2000, as compared with 328.4 such articles in the five years through to 2012. Third, in the early period from 1991 to 1998 the bulk of the literature linking autism to this set of genetic mutations—175 out of 307 papers, or 57%—featured fragile X as a keyword. Finally, from 1998 onward—coinciding with the formation of AGRE and increased funding—the share of fragile X papers decreased to 35%, even as it grew considerably in absolute terms. That is, there was an explosion of research on the link between ASDs and other genomically designated conditions. In other words, it was only after the conditions of possibility described earlier were in place and after further diagnostic expansion of autism that associations between autism and other genetic disorders took off.

Given the relatively high rate of autism keywords in 1991, it is worth tracing the literature back further. Web of Science keyword capture was

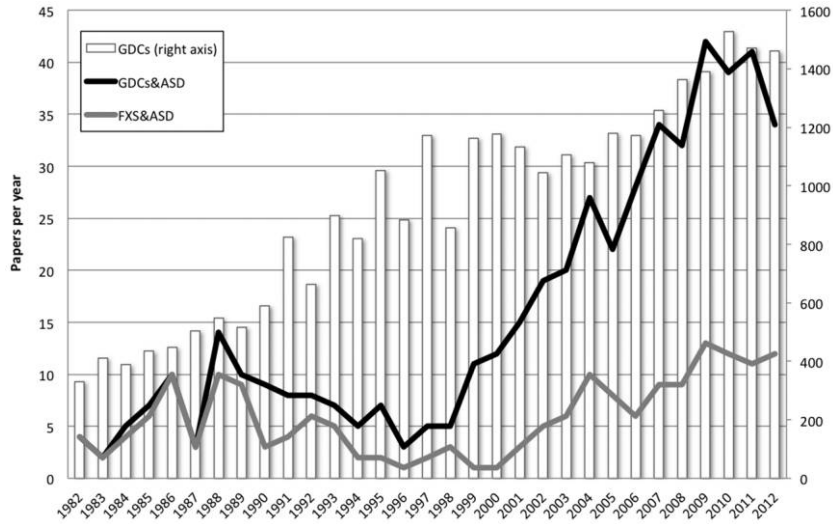

FIG. 3.—Papers with titles related to genomically designated conditions and the subset with autism and fragile X title terms by year, 1982–2012.

limited before 1991. Figure 3 therefore reports the same search string for title terms rather than keywords. Here we see even more clearly that studies of fragile X dominated the early research on autism and genetically specific developmental disorders: from 1982 to 1998 almost 68% of the 112 papers in the data set with autism in their title also had fragile X in the title. By contrast, between 1998 and 2012 only 28% of the 376 papers had fragile X in their title. The centrality of fragile X is particularly pronounced before 1990 when it featured in 48 of the 55 papers with autism in their title.[21] These results further indicate that fragile X research paved the way for other genomically designated conditions to become associated with autism, but in order to isolate actual from observed genetic heterogeneity we must turn to ASD rates in those conditions over time.

Snapshot of 13 Syndromes

Table 1 tracks the association between autism and 13 strategically selected genetic mutations. Using the list compiled by Betancur (2011), we extracted all and only those genetic disorders that fit three criteria: (1) they are diagnosed

[21] Of the remaining seven papers, four were about the contrast between autism and Down syndrome (which is now associated with ASDs; see Betancur [2011, p. 59] for a summary and list of relevant studies); i.e., they were not about a linkage between autism and a mutation. This further confirms fragile X's centrality in the early research.

TABLE 1

HISTORIES OF AUTISM ASSOCIATION IN 13 GENOMICALLY DESIGNATED CONDITIONS

SYNDROME/LOCUS	MUTATION REPORTED	FIRST COGNITIVE PHENOTYPE*	FIRST AUTISM REPORT†	PRE-1990		1991–2000		2001–12	
				Mean ASD Rate (%)	No. of Studies	Mean ASD Rate (%)	No. of Studies	Mean ASD Rate (%)	No. of Studies
FXS/FMR1 CGG, Xq27.3	1969	1969	1980	22.2	13	21.5	6	41.7	28
WAGR/11p13 deletion syndrome	1978	1978	1995	NA	0	NA	0	29.9	3
22q13 deletion syndrome	1988	1988	2000	NA	0	NA	0	38.7	6
22q11.2 deletion syndrome	1981	1982	1998	NA	0	NA	0	30.4	10
Cri du Chat/5p− syndrome	1963	1963	1994	NA	0	NA	0	39.6	2
Williams syndrome/7q11.2 deletion	1993	1993	2006	NA	0	NA	0	26.0	3
Smith-Magenis/17p.11.2 deletion	1982	1984	1986	NA	0	NA	0	76.0	2
Potocki-Lupski/17p.11.2 duplication	1991	1992	2000	NA	0	14.3	1	51.7	2
2q37 deletion syndrome	1989	1989	1992	NA	0	12.5	1	52.7	2
XYY syndrome	1961	1962	1971	NA	0	NA	0	37.4	7
XXYY syndrome	1961	1961	1977	NA	0	NA	0	41.4	4
Klinefelter/XXY syndrome	1959	1959	1999	NA	0	NA	0	17.2	9
Turner/monosomy X syndrome	1959	1959	1997	NA	0	3.5	2	0	1
Total					13		10		79

NOTE.—In order ensure that we are capturing ASD rates and reports of cognitive phenotypes in research on genetic mutations, we are only considering cases confirmed by molecular diagnosis. In the cases of the 7q11.2 deletion (Williams syndrome) and 22q11.2 deletion (which accounts for most cases of DiGeorge, velocardiofacial, and several other rare clinical syndromes), this means excluding research in which subjects were selected according to older, clinical diagnostic criteria and therefore may not have had the mutation in question. Thus, there were other reports of ASD in atypical cases of Williams syndrome, but the first to be molecularly confirmed (as most Williams syndrome cases were after 1995) was a 2006 case study (Herguner and Motavalli Mukaddes 2006).

* Mean lag = .4 years.

† Mean lag = 16.6 years.

if and only if a specific mutation is observed in a patient, (2) the mutation was reported at least 15 years ago, and (3) there are two or more papers that report ASD rates in a cohort of probands (i.e., people with the relevant mutation) with the disorder, rather than just case reports. The first criterion ensures that we are only analyzing the histories of genomically designated conditions, which is to say syndromes that are rigidly designated by a genetic mutation (Navon 2011). As explained in the appendix, this is why we exclude genetic disorders like Rett syndrome and tuberous sclerosis from our analysis.[22] The second criterion allows us to trace these mutations over the period that witnessed a transformation in diagnostic practice, research orientation, and biosocial activism. Finally, the third criterion ensures that the association between any given mutation and autism is not an artifact of a small number of case reports or a single paper reporting rates.

For each genetic condition, one of the authors and a research assistant separately created a Web of Science string that included all of its major synonyms and those of its underlying mutation. Next, we identified the first paper reporting the mutation in question and the first paper reporting the association of a "cognitive phenotype"—usually some form of developmental delay. Then, we went through every paper on the condition with an autism-related keyword. First, we identified the earliest published association between the mutation and any form of autistic disorder (autism, infantile autism, ASD, PDD-NOS, or childhood schizophrenia), usually in the form of a case report. Finally, in papers in which a cohort of five or more unrelated probands underwent psychiatric evaluation that included examination for autistic disorders (but was not selected for them), we checked for reported autism or ASD rates and recorded every such case.[23] We report the mean ASD rate and number of papers reporting ASD rates before 1990, in 1991–2000, and in 2001–12. In addition, for all of these fields, we checked any citations to previous studies that were not captured

[22] Thus, we include cases of Williams syndrome, which had clinical diagnostic criteria before it was redelineated according to the 7q11.2 microdeletion in the 1990s, because studies of ASD rates almost always confirm the presence of the 7q11.2 microdeletion in research subjects. By contrast, we exclude Down syndrome from this analysis because most studies do not confirm trisomy 21 status. The history of the autism–Down syndrome association dates to 1979 (Wakabayashi 1979) and warrants its own detailed analysis, but like other genetic disorders discussed in this article, average ASD rates in Down syndrome studies have risen severalfold since 2000.

[23] When the same cohort or substantially the same cohort is discussed in multiple papers, we report it as one study. We limit our reporting of ASD rates to patients receiving a formal ASD diagnosis or currently meeting an ASD cutoff score on a diagnostic or screening instrument, rather than rates of patients with "autistic features" or those who have met ASD criteria in the past, which is often far higher. In studies in which a screening instrument was followed up with a diagnostic evaluation, the rate for the diagnostic evaluation was reported.

by our Web of Science search string, in order to ensure that we were identifying the first paper to report the mutation, its first association with a cognitive phenotype, its first association with autism, and as many reports of ASD rates in cohorts of probands as possible.

The first striking pattern in table 1 is that almost all these mutations were first associated with what we are calling a "cognitive phenotype" (to hark back to Folstein and Rutter's terminology)—that is, some kind of psychiatric observation or diagnosis, most often MR or developmental delay—well before they were associated with autism. This association with a cognitive phenotype often came in the same paper that reported the mutation (nine out of 13 cases) or very shortly thereafter (four cases), with a mean "lag" time of 0.4 years. Put differently, most of these mutations were first observed in children who came to medical attention because of developmental delay alongside various congenital abnormalities.

Second, in contrast to the typically very short or nonexistent gap between discovering the mutation and associating it with a cognitive phenotype, there is generally a long lag before autism is reported in probands, with a mean of 16.6 years. In 2q37 deletion syndrome it only took three years, and Smith-Magenis syndrome only four, but those were among the most recently discovered mutations (1989 and 1982, respectively). For XYY it took 10 years (1961–71), but as we see below, it was another 13 years before a report of autism in an XYY proband was ascribed anything more than incidental significance. In most cases it took well over a decade, and for the 5p−, Klinefelter/XXY, and Turner syndromes (monosomy X) it took over 30 years. Yet, the literature makes it clear that research subjects with genomically designated conditions were being evaluated for and having existing psychiatric diagnoses noted, and therefore that autism would likely have been reported when it was encountered. Indeed, when an association with autism was first noted, usually in a case study, it was often published in a leading journal, demonstrating that finding autism in genomically designated probands was considered a significant finding and was not likely to have been simply missed or ignored.

The third and most striking pattern is that for all mutations but one there was a marked increase over time in reported autism rates, mostly taking place after 2000. With the exception of FXS, we found no reports of autism rates in research cohorts before 1990, even though most of the mutations (11 of 13) were discovered earlier. During the 1991–2000 period, while there were several case studies reporting single associations with autism, just four studies reported autism rates in three syndromes other than FXS. From 2001, however, autism diagnoses have been reported in significant proportions of people with genomically designated conditions other than fragile X. In nine syndromes with no reports of ASD rates before 2001, average rates of 17.2%–76% across 46 studies have since been reported. In the three

other cases (excluding fragile X), we go from ASD rates of 3.5%, 12.5%, and 14.3% in four studies before 2001, to mean ASD rates of 0%, 52.7%, and 51.7%, respectively, across five studies since.[24]

We argue that this trend, which is also reflected in the review literature on autism genetics, constitutes strong evidence that the actual genetic heterogeneity of autism increased over time.[25] How large was this increase? The 13 disorders listed in table 1 cannot, by themselves, account for much of autism's prevalence, heritability, or overall genetic heterogeneity. This is not our claim. We take this trend to be evidence for the fourth loop we described earlier: as autism's diagnostic criteria were broadened, the ASD population expanded to include a greater phenotypic range and therefore many more individuals who previously would not have been diagnosed with autism, bringing new mutations hitherto unassociated with autism into the fold. But this was not simply the result of autism risk rising evenly throughout the population or the random accrual of common genetic variants. Practically all of the 179 mutations listed by Betancur (2011) are rare. Our 13 cases represent a unique subset of those 179 rare mutations: they have been known to human geneticists for years—and in several cases decades—as highly penetrant causes of developmental disorder, and yet before 2001 almost no one in whom they were observed was reported as being diagnosable with autism. From 2001 onward, however, individuals carrying these mutations were being diagnosed with ASDs, thereby increasing autism's genetic heterogeneity. Crucially, as we argued earlier, they go from little or no association with ASDs to rates that, given ASD prevalence, could not possibly be found in any common genetic variant. As the case

[24] The two reports of low ASD rates in Turner/monosomy X syndrome in the 1990s were animated, in part, by the idea that girls with a paternally inherited X chromosome would be more likely to be autistic (apparently they were; see Creswell and Skuse 1999). More recently, the prevailing line of thought is that Turner syndrome girls have deficits in social and cognitive functioning but not on the same level as ASDs (Elgar, Campbell, and Skuse 2002; Lawrence et al. 2003). This informed the two cohort studies reporting ASD rates of 0% in recent years.

[25] To test the robustness of these results, we conducted a survey of review articles in the literature on autism genetics. A small number of these reviews began discussing associations between autism and a handful of chromosomal abnormalities in the mid-1980s, but with the exception of fragile X they remained limited to summarizing isolated case reports (see Reiss et al. [1986] for the most thorough example). By the late 1990s and early 2000s, by contrast, there were many more review papers discussing the relationship between autism and genetic disorders and in much greater detail (e.g., Gillberg 1998; Folstein and Rosen-Sheidley 2001; Bespalova and Buxbaum 2003; Veenstra-VanderWeele, Christian, and Cook 2004; Cohen et al. 2005; Vorstman et al. 2005). The reviews also typically note that the mutations under discussion were first identified in association with some form of developmental delay, before later being found in people who are diagnosable with an ASD. Our survey of reviews thus confirms the main findings reported in table 1.

studies below demonstrate, this is a story not about autism rates rising evenly throughout the population but about very particular trajectories of diagnostic change driven by the looping processes we described earlier.

In order to sketch these multiple trajectories through which diagnostic expansion has contributed to autism's genetic heterogeneity, we present abbreviated case studies of three different genomically designated syndromes' associations with ASDs over time: Phelan-McDermid/22q13 deletion syndrome, Williams syndrome, and XYY syndrome.

Phelan-McDermid Syndrome

When someone has a deletion at site q13.3 on the long arm of the twenty-second chromosome, they are diagnosed with 22q13 deletion syndrome, now known as Phelan-McDermid syndrome (PMS). While there are no clinical diagnostic criteria, most people with PMS have moderate-to-severe ID and severe language delays and are also likely to suffer from a subset of a long list of associated symptoms. As with fragile X, autistic behaviors are common. However, even though MR was considered a core feature of the 22q13 deletion from its discovery in the late 1980s (see Phelan, Rogers, and Stevenson 1988; Phelan et al. 1992; Hinkel et al. 1997; Wong et al. 1997), it was another 12 years before an association with autism was even noted in the literature (Goizet et al. 2000). In 2001, the medical geneticist most associated with PMS, Katy Phelan, agreed that most cases display significant "autistic features" but specifically ruled out a comorbid autism diagnosis: "It is somewhat difficult to make an additional diagnosis of autism for children with severe to profound mental retardation. . . . To be diagnosed with autism there must be qualitative differences in language and socialization when compared to non-autistic children with retardation of similar degree. With a cognitive age equivalent of 9.3 months, these children are expected to show some autistic-like features. All children in this sample appear to have language and socialization skills consistent with their general mental ability" (Phelan et al. 2001, p. 95). Phelan made a nearly identical assertion two years later (2003, p. 2). Essentially, she agreed with the critics of Hagerman and Rimland's studies from the mid-1980s, who argued that the rates of autism in FXS were no different from those in IQ (cognitive age) matched controls. She was also saying that a diagnosis of autism was superfluous given the severe delays associated with the mutation. The issue is not whether the children manifested some "autistic traits" but whether an ASD diagnosis added to or better characterized a genetic disorder already associated with severe developmental and linguistic delays.

And yet by 2008, Phelan had conditionally abandoned her reluctance to countenance ASD diagnoses in 22q13DS patients, as long as they were cordoned off as "syndromic autism": "Behavioral features of Phelan-McDermid

syndrome include poor eye contact, stereotypic movements, decreased socialization, and language impairment consistent with autism spectrum disorders. . . . *Deletion 22q13 has been shown to be one of the common chromosome defects associated with autism.* The term 'syndromic autism' has been suggested for autism accompanied by dysmorphic features and the 22q13 deletion syndrome was cited as an example of a genetic disorder characterized by autistic behaviour" (Phelan 2008, p. 14; our emphasis). Reported rates of autism in PMS are now consistently in the 40%–80% range (see Sarasua et al. 2011), while 22q13.3 deletions are estimated to account for around 1% of all ASD caseloads, with mutations in the key gene at 22q13.3, SHANK3, accounting for perhaps another 1% (Abrahams and Geschwind 2008, p. 344).

Why did Phelan change her mind? The capacity to refer to autism as a spectrum composed of autistic behaviors that can be diagnosed alongside ID is clearly a condition of possibility for accepting the meaningful association between autism and 22q13DS. However, formal diagnostic expansion cannot be the proximate cause, since Phelan's initial rejection of the statement was in 2001, seven years after DSM-IV. The same goes for the other condition of possibility noted earlier, namely, the reorientation of genetics research around pathways and intermediate objects. What is more likely is that between 2003 and 2008 Phelan changed her mind in response to the increased acceptance of what she and others call "syndromic" or genetically specific autism and the broader turn to diagnose autism in patients whose autistic symptomatology was well explained by moderate-to-severe ID.

There is also reason to believe that the formation of a biosocial community around 22q13DS, inspired by the increasingly successful and well-recognized example of fragile X, played a role in changing Phelan's thinking about the 22q13.3 deletion and autism. A parents' group for 22q13DS was formed in 1998 with Phelan's assistance, and it became the Phelan-McDermid Syndrome Foundation (PMSF) in 2002. As with fragile X, this parent-led advocacy organization maintains close ties to researchers—especially Phelan—and works assiduously to secure research funding and steer research toward goals it deems important. Given PMS's rarity, it is crucial for PMSF to emphasize the link to ASDs and to offer its disorder as a genetic model for autism. After a presentation that reported an ASD rate of 78% in a PMS sample, Phelan exclaimed approvingly: "That's amazing. . . . It makes 22q13 very appealing because [there is] so much interest and money available (I shouldn't say money); but autism is so hot right now, to have a community where you have a defined, identifiable cause of their autism is [a] luxury . . . you have an identified genetic cause of autism and you have . . . a defined group of individuals that are eager to participate in a study to learn more about their condition . . . is I think an autism researcher's dream come true. So it is definitely beneficial to the researchers

and it's beneficial to the families" (personal interview with Katy Phelan, New York, March 2011).

It is clear why giving an autism diagnosis to individuals with 22q13DS was no longer superfluous: the high risk of an ASD diagnosis conferred by the 22q13.3 microdeletion helped PMSF to attract research interest and funds on a scale that would have been otherwise unimaginable for such a rare disorder. We do not mean to claim that Phelan or PMSF leaders were being disingenuous. It is simply that they have learned to speak a new language—the local language of the trading zone and the final common pathway. That said, it is undeniable that they saw the exchange as a mutually beneficial one. As one of the PMSF leaders told us (personal interview, New York, 2011): "You know, this autism connection has just changed our lives, totally changed our lives." At the same time, she was also keenly aware that PMS is an autism geneticist's "dream come true." Indeed, autism geneticists are especially interested in 22q13.3 not only because SHANK3 indicates a plausible biochemical pathway of disruption in brain development (Kouser 2011) but also because PMSF is able to deliver a "defined group of individuals that are eager to participate in a study" (personal interview with Katy Phelan, New York, 2011).

For these reasons, an alliance has formed between PMS parents, advocates, and researchers, on the one hand, and their counterparts concerned with autism, on the other. The two groups came together, for example, in a 2011 International Phelan-McDermid Syndrome Symposium, coorganized by the PMS Foundation and Joseph Buxbaum, a leading expert on autism genetics from the Seaver Autism Center at Mount Sinai. All the leading PMSF advocates and researchers were there, as well as 60 autism researchers and about 40 advocates and leaders of autism organizations such as Autism Speaks and the Simons Foundation. SHANK3 has become what Autism Speaks called "the new 'it' gene for autism" (Kouser 2011), and research aimed at a PMS pharmaceutical product in the first instance, and ASDs more generally in long run, is underway. In short, groups like PMSF are consciously and pragmatically drawing on the model pioneered by fragile X researchers and advocates (the symposium included a talk subtitled "Lessons from Fragile X"): leverage the overlap between your specific genetic disorder and autism to attract research interest, funding, and recognition and organize your community in such a way so as to facilitate that research. With this in mind, PMSF is seeking to establish a registry for researchers modeled on AGRE, develop emotional ties to researchers, and begin funding postdocs (PMSF leader, personal interview, New York, March 2011). At the same time, autism organizations—led and directed by autism parents—remain heavily invested in genetics research and thus in conditions like fragile X and PMS that offer the promise of a genetic model for ASDs.

Williams Syndrome

Although originally a clinical diagnosis, Williams syndrome is now delineated according to a deletion at site 11.23 on the long arm of the seventh chromosome (Nickerson et al. 1995; Donnai and Karmiloff-Smith 2000).[26] Williams syndrome represents perhaps an even more decisive confirmation of the looping argument: it is associated not only with moderate ID, cardiac problems, and a distinctive facial phenotype but also with a distinctive trait of "hypersociality" and strong relative strengths in language and musicality. Indeed sociability and strong language skills led some to describe Williams syndrome as the "antiautism"—a developmental disability with a strikingly different behavioral and cognitive profile from classic autism. As Jones et al. put it (2000, p. S41), "Individuals with WMS and those with autism represent two polar opposite groups in terms of social behavior." They explain (p. S44): "WMS children seek out social interaction and eye contact and, generally, do it in a polite and friendly manner. . . . In contrast, the cardinal feature of autism is a profound deficiency in social knowledge, affective expression, and communication." In short, as late as 2000, the behavioral phenotypes of Williams syndrome and autism were seen as almost mirror opposites of one another.

Before 2000 there were six reported cases of behaviorally atypical and molecularly unconfirmed cases of Williams syndrome in which an ASD diagnosis was suggested, and the two studies that reported them (Reiss et al. 1985; Gillberg and Rasmussen 1994) had very little impact on the field. The prevailing view remained that autism and Williams syndrome were strikingly divergent, such that "future studies examining the neuroanatomical differences between WMS and Autism may reveal clues to aspects of the neural and genetic bases of social behavior" (Jones et al. 2000, p. S44; see also Einfeld, Tonge, and Rees 2001).

But while early discussions emphasized the differences between autism and Williams syndrome, today the two are increasingly reported as comorbid diagnoses. As we saw in table 1, the mean rate of ASD diagnoses in three studies of molecularly confirmed Williams syndrome patients during 2001–12 was 26%. How did it become possible for these "polar opposite" diagnoses to overlap to such an extent? The answer is that the "overfriendliness" of individuals with Williams syndrome—their easygoing manner in approaching others and holding a conversation—are now interpreted as merely apparent evidence of social skills and empathy. On closer

[26] This entails both excluding the minority of people who had been clinically diagnosed with Williams syndrome but lack the 7q11.23 deletion and including others who would have been unlikely to receive the prior clinical diagnosis but have the deletion. The Williams Syndrome Association takes the same position: http://www.williams-syndrome.org/diagnosing-williams-syndrome/diagnosing-williams-syndrome.

scrutiny, their behavior reveals that, while they may be well attuned to social cues, they are impaired in their capacity to reason about the mental states of others: "social perception was spared in comparison with other neurodevelopmental disorders, but social cognition was not" (Laws and Bishop 2004, p. 45; see also Tager-Flusberg and Sullivan 2000). By disaggregating social perception and cognition in Williams syndrome, with the former an area of strength that creates the appearance of strong social skills and the latter a relative weakness, researchers were able to point to behavioral characteristics that do resemble autism, such as "problems with establishing friendships," "disinhibition and social isolation," as well as "pragmatic language impairment (PLI), including excessive chatter, the propensity for socially inappropriate statements and questions, and for talking to themselves," and generally not being well attuned to the conversational partner (Laws and Bishop 2004, p. 45).

In this view, individuals with Williams syndrome suffer from "social difficulties" that are similar to those of the "active, but odd" type described by Wing and Gould (1979) as part of the autism spectrum. The superficial opposition between the two conditions resolves into a common underlying deficit in pragmatic language skills and social cognition: "Far from representing the polar opposite of autism, as suggested by some researchers, Williams syndrome would seem to share many of the characteristics of autistic disorder" (Laws and Bishop 2004, p. 45). That is, people with Williams syndrome may be friendly and social, but they struggle to establish and maintain a group of friends; they may initiate lots of conversations but in the wrong sort of way.

Whatever one thinks about this reasoning, in which so much hangs on distinguishing "social perception" from "social cognition" as two independent "modules," it is patently clear that it would have been impossible to make these fine distinctions and link Williams syndrome to ASDs if autism's diagnostic criteria were not significantly broadened and transformed. Kanner's "autistic aloneness" could never have been mistaken for Williams syndrome's "problems with establishing friendships." Excessive chatter or the inappropriate choice of words and topics could not have been meaningfully likened to autism if it had not become a spectrum of impairments in pragmatic language and social interaction. The association between Williams syndrome and autism therefore serves as evidence of a larger process: it is not only that autism became diagnostically defined as an impairment of social interaction but more importantly that it has become widely understood—by experts, clinicians, doctors, teachers, therapists, parents, advocates, even autistics themselves—as a deficit in some subtle cognitive mechanism that makes us social beings, that allows us to read and emit social cues unawares, whether this mechanism is understood as a "theory of mind" (Baron-Cohen, Leslie, and Frith 1985) or what have you. Parents, teachers,

and clinicians operating on this understanding have diagnosed many children with ASD who in the past could not possibly have been given this diagnosis, bringing new populations, and therefore many new mutations, into the autism population.

In this way, we have gone from Williams syndrome and autism as "polar opposite groups" to a study that found autism in three of 30 children with "geneticially confirmed Williams Syndrome" and ASDs in a full 50% of the 30 cases (Klein Tasman et al. 2009, p. 90). Thus, in Betancur's summary (2011, p. 55), "50% of patients with Williams syndrome meet the diagnostic criteria for ASD." As with fragile X and PMS, the biosocial community organized around Williams syndrome is seeking to leverage the overlap with autism into research funds and attention. A $5.5 million National Institute of Child Health and Human Development (NICHHD) grant to study Williams syndrome and its lessons for genetics and human behavior more generally had the Williams Syndrome Association's executive director, Terry Monkaba, exclaim on ABC News: "Our 15,000 kids may hold the key to helping millions with autism. . . . What a great legacy!" (cited in Lovett 2012).

XYY Syndrome

Autism's diagnostic expansion at the "high-functioning" end of the spectrum has also increased the scope for associating genomically designated syndromes and ASDs. Take the case of XYY syndrome. Despite its infamous beginnings as a biomedical category in the 1960s and 1970s when it came to be associated with aggression and antisocial behavior in the guise of a "Supermale" syndrome (see Richardson 2013, pp. 84–90), in recent decades XYY syndrome (i.e., males with an extra Y chromosome) has been primarily associated with moderately increased stature, acne, and an IQ around 10 points lower than that of an unaffected sibling or SES–matched controls (e.g., Leggett et al. 2010; Ross et al. 2012). XYY is not as rare as Williams or 22q13.3. It is found in around one in 1,000 male births, so it is hardly surprising that there were a couple of case reports of autism in people with an XYY karyotype in the 1970s (Abrams and Pergament 1971; Nielsen et al. 1973; Gillberg, Winnergard, and Wahlström 1984). Researchers, however, were unanimous that the association was "most probably coincidental" (Nielsen et al. 1973, p. 22).

Yet, when we fast-forward to the period since 2001, we find seven studies reporting a mean ASD rate of 37.4% in XYY cohorts (see table 1). Unsurprisingly, this link was forged by the same group of blacksmiths: the argument that XYY might be a genetic cause of autism was first advanced by Christopher Gillberg, who was also among the first to link autism to both Williams syndrome and FXS (e.g., Gillberg et al. 1984). Just like the

1970s researchers, he was reporting on a single case study in which an XYY proband also qualified for the diagnosis of infantile autism based on "Rutter's (1978) and DSM-III criteria (1980)" (Gillberg et al. 1984, p. 354). However, Gillberg did not consider the association to be incidental. He connected XYY to autism in two ways. First, drawing on Lorna Wing and Simon Baron-Cohen's speculations that autism is somehow linked to maleness, he implicated the existence of an extra Y (i.e., "male") chromosome. Second, he accounted for the fact that so few cases of XYY were found to be diagnosable with autism by resorting to the idea of a spectrum of autistic-like behaviors, ranging from severe to mild (p. 358; our emphasis): "The XYY karyotype may predispose the child to speech-language delay, difficulties in establishing social relationships, and overall immaturity of brain development. All these features . . . are typical of autism, *but in autism there is another dimension to the problems, regarding severity and quality*. The XYY constitution per se does not cause autism, but rather might predispose the boy to milder disturbances of the kind seen in 'the triad of language and social impairment' described by Wing and Gould (1979)." For XYY syndrome, as with FXS and heritability studies, a broader spectrum made it easier to associate autism with a genetic underpinning. Still, in the mid-1980s Gillberg's speculation still seemed far-fetched, and nobody bothered to follow up on it for over 20 years.

Beginning in 2003, a series of XYY cohort studies began to report autism rates. A paper by Tartaglia et al. (2007; leading fragile X expert Randi Hagerman was a coauthor) found 36%, or 8 of 22, cases diagnosable with an ASD—one with autism and seven with PDD-NOS. A 2011 study found that 11 of 58 cases of XYY syndrome had an ASD, while "communicative profiles indicative of mild autistic features were common" among the remainder (Bishop et al. 2011, p. 954). Finally, in 2012 a pair of studies found that half of a sample of 40 already had an ASD diagnosis, while nine of the remaining 20 were in the mild-to-moderate range (Cordeiro et al. 2012; Ross et al. 2012). Rather than seeing merely a "coincidental association," a recent paper by Roeltgen and Ross (2010) called XYY "a possible model for autism spectrum disorder." No less important, this association serves to reinforce the very theory that Gillberg invoked in order to attribute significance to a single case of XYY/autism comorbidity in 1984, namely, that autism is a male disorder and that the 4:1 ratio is real and biologically grounded.

CONCLUSION

We have argued that looping dynamics can reverberate among diagnosis, geneticization, and the genetic makeup of populations. Looping processes must therefore be grappled with if we are to truly understand the findings

emanating from human genetics, in particular, and investigations into the biological basis of human difference more generally. In the case of autism, we saw how geneticization played an important role in autism's secular diagnostic expansion. Then we presented evidence based on ASD rates in genomically designated conditions to support the claim that this same diagnostic expansion produced the vast genetic heterogeneity now taken to be a biological fact about autism. We also followed three trajectories of diagnostic expansion that brought genomically designated conditions, which is to say rare, highly penetrant (if variable) genetic mutations, into the autism population: from MR to a comorbid diagnosis of autism in the case of 22q13 deletion syndrome, from hypersociality and relative strengths in language to autistic difficulties in social communication in the case of Williams syndrome, and from mild behavioral challenges and slightly depressed IQ scores to high ASD rates in XYY syndrome. In each case, there can be little doubt that the high ASD rates now seen in these disorders—rates than have increased many times more than in the general population—would have been unthinkable 20 years ago, never mind to Kanner. The same is most likely true of the other syndromes in table 1. The three case studies, plus the detailed analysis of the pioneering case of FXS, served to confirm our argument that changing diagnostic practices—made possible by acceptance of ASD/ID comorbidity, the focus of research on intermediate pathways, and the mutually beneficial transactions between biosocial communities—have brought multiple new mutations into the autism population.

But could it be the case that some kind of environmental or epigenetic factor was interacting with these and many other mutations, thereby explaining autism's increased prevalence and genetic heterogeneity? Consider the contrast with ID: reported rates of ID/MR in 22q13 and Williams syndrome have been very high ($\geq$90%) since their discovery. XYY has been widely understood to cause mildly decreased IQ scores since the early to mid-1970s, as have other sex chromosome disorders like the XXYY and XXX syndromes that have similarly come to be associated with ASDs. FXS has been considered, since its discovery, to be a genetically specific form of X-linked MR. Finally, MR has always been considered a core feature of most other genetic disorders that have recently come to be associated with autism: 5p− syndrome, the 17p.11.2 duplication and deletion syndromes, and 2q37 deletion syndrome from table 1, as well as Down syndrome, 1p36 deletion syndrome, 11p11.2 deletion syndrome, Angelman syndrome, Prader-Willi syndrome, tuberous sclerosis, and many other genetic disorders that are now thought to cause high rates of autism in their bearers. Simply put, we are not aware of a plausible biological mechanism that can explain why these mutations have displayed fairly constant associations with ID/MR but such a sudden spike in ASD rates across disparate geographical and national contexts.

By contrast, we have presented evidence to suggest that a looping mechanism that involved diagnostic expansion can explain the dramatic shift in ASD rates in people with genetic mutations alongside stable MR rates. That these mutations strongly predispose their bearers to ASDs and autistic behavior is, we have argued, dependent on an understanding of autism that has been transformed, in part, by the very drive to "geneticize" it. In this way, looping led to powerful associations between autism and a host of highly penetrant genetic mutations, most of which were already known to cause the kinds of complex cognitive and developmental impairments and congenital abnormalities that have attracted the avid attention of human geneticists since at least early 20th-century eugenics. This is how autism was transformed from a relatively rare condition associated with very few genetically specific disorders into a highly prevalent and extremely genetically heterogeneous condition. This article therefore provides orthogonal confirmation of the finding that diagnostic expansion was a major driver of autism's increased prevalence (Shattuck 2006; King and Bearman 2009; Eyal 2013): when we hold a series of "autism genes" constant, we see that they had no meaningful association with autism for years until changing diagnostic criteria led to high ASD rates among their bearers.

This finding compels us to consider the social processes that can transform the genetic makeup of populations and shift the ground beneath researchers' feet. On the one hand, it is hardly surprising that changes in diagnostic practice can affect the etiological findings associated with a medical condition. On the other, this means that—their supposedly foundational etiological status notwithstanding—what genes are taken to be causes of is contingent on shifting social and classificatory terrain. Let us be clear: this is not an argument about the "social construction" of genes. Just because autism's genetic heterogeneity is not a timeless biomedical fact but rather the outcome of a complex series of looping processes in which genetics itself played a key part does not mean that our contemporary understanding of autism genetics is less "real."

This is a key analytic advantage of dynamic nominalism: it allows us to treat knowledge about human difference as a genuine sociotechnical phenomenon that can both shape and be shaped by actors over time (Hacking 1995, 2007; Kuorikoski and Pöyhönen 2012). Moreover, to the extent that genetic findings inform the thinking of relevant actors (patients, parents, doctors, clinicians, advocates, etc.) and come to shape diagnostic practice, they also initiate looping processes. In this case, the idea of autism as a genetic disorder turned out to be, in part, a self-fulfilling prophecy as genetic evidence served to influence diagnostic practice. However, the geneticization of autism also led to unintended consequences as genetic heterogeneity, rather than clarity, was the ultimate outcome. Today, new looping processes are unfolding as these previously unrelated mutations are mobilized

as models for ASD research, leading our understanding of autism and our knowledge about genetics into new dynamic entanglements. All this demonstrates that genetics research does not stand outside its objects of analysis, particularly when it comes to categories of psychiatric and childhood developmental difference. Rather, ideas about genetic etiology can become intertwined in complex social processes that loop back upon the genetics findings, sometimes confirming them, sometimes undoing them, and often pushing them in unexpected directions that render the "genetics of x" a moving target.

Future research should therefore extend our analysis to other conditions, and especially to other fluid categories of childhood behavioral, learning, and developmental difference. Autism's diagnostic expansion may be unique in its degree, but it is not unique in kind, and the genetic heterogeneity of disease categories now appears to be the norm in postgenomic research. For example, conditions like ADHD have likewise grown by orders of magnitude and are increasingly characterized by high heritability estimates and genetic heterogeneity (e.g., Lo-Castro, D'Agati, and Curatolo 2011; Schachar 2014). It stands to reason that looping processes have also played a role in ADHD genetics, although given the availability of pharmaceutical treatments and the fact that it is a relatively mild behavioral syndrome, we would expect these processes to be quite different from the case of autism. Differences notwithstanding, our analysis of autism suggests that social and biomedical scientists should take stock of the impact that genetics findings can have on other biosocial communities and therefore on the way that populations of people are delineated, understood, and acted on.

Sociology therefore has an important contribution to make to the broader project of uncovering the biological bases of human disease and difference: in order to properly understand the flood of findings from genetics research, we must situate them with respect to variable, inherently sociotechnical practices of classification and the looping processes that have made and remade them into what they are today. Indeed, this article has shown how the very move to understand autism as a genetic condition contributed to the spirals of looping that turned it into an extraordinarily genetically heterogeneous condition. As researchers aim to uncover the genomic basis of different categories of human difference, we should therefore keep in mind that they are aiming at moving targets (Hacking 2007), and ones that can in fact be moved by the very attempt to ascribe and uncover a genetic etiology.

APPENDIX

Scientific Papers

We chose to use ISI's Web of Science for the analyses reported in this article because a topic search for "autis* OR ASD*" returned almost 10,000 more results than one conducted in PubMed (the other major database covering biomedical research). In addition, the ability to use complex Boolean search strings to sort papers and especially to trace citations in Web of Science in order to identify foundational papers was crucial for several of the analyses reported below. Using a single authoritative database in order to capture a field of research in the sociology of science and knowledge is a well-established research strategy (e.g. Shwed and Bearman 2010; Vilhena et al. 2014). Given how much more comprehensive Web of Science is in comparison to PubMed, we are confident that the payoff in searching an additional database is negligible.

We used the following search string:

> TS=("FRAGILE X" OR XQ27* OR1p36* OR 1q21* OR 2p15–p16* OR 2q23* OR 2q338 OR 2q32q33* OR 2q37* OR 3q29* OR "Wolf–Hirschhorn" 4p16.3* OR 4q21* OR "Cri du Chat" OR 5p-* OR "5P minus" OR 5q14* OR "Sotos syndrome" OR 5q35* OR 5q35.2q35* OR "Williams syndrome" OR "Williams-Beuren syndrome" 7q11* OR 8p23* OR"9q subtelomeric Deletion" OR "Kleefstra Syndrome" OR 10p14p15* OR "10q22–q23 deletion" OR "Distal 10q deletion" OR 11p15* OR "Beckwith-Wiedemann" OR "Silver-Russell syndrome" OR "WAGR syndrome" OR 11p13* OR "Potocki-Shaffer" OR 11p11* OR "Jacobsen syndrome" OR "11q* deletion" OR "Angelman* syndrome" OR "Prader-Willi" OR "15q11–q13" OR 15q13* OR 15q24* OR 15q26* OR "Rubinstein–Taybi" OR 16p13* OR "16p11.2–p12.2" OR 16p11* OR 17p13* OR "Miller-Dieker" OR "isolated lissencephaly" OR 17p13* OR "Smith-Magenis" OR "Potocki-Lupski" OR 17p11* OR NF1* OR 17q11.2* OR 17q12* OR17q21* OR "Down* syndrome" OR "trisomy 21" OR "velocardiofacial" OR VCFS OR "VELO-CARDIO-FACIAL" OR "DiGeorge Syndrome" OR 22q11* OR Phelan-McDermid*, 22q13* OR Xq28* OR MECP2 OR "Turner* syndrome" "monosomy X" OR "Klinefelter" OR XXY OR XYY OR XXYY OR "45,X/46,XY Mosaicism"

We restricted the search to articles because Web of Science does not collect keyword data on reviews, letters, and other kinds of publications. For figure 3, which refers only to titles, we used the same search string but include articles, editorial material, reviews, letters, and proceeding papers. It should be noted that this string captures many papers—for example, gene mapping at 15q24 rather than studies of the 15q24 deletion—that we would not expect to have any relation to the genetic disorders associated with ASDs, and therefore the rates reported below should be read in rel-

ative terms and as an extremely conservative estimate of autism's status in the pertinent fields.

Mutations

We have relied on the list provided by Betancur as the most comprehensive, up-to-date meta-analysis of genetic disorders and mutations associated with autism. Since the first version of this article was completed, a new comprehensive list has been compiled by Pinto et al. (2014) (Betancur was one of the coauthors). We have opted not to use it because it includes all the mutations listed by Betancur, while adding others that are only recently (and often tenuously) associated with autism. Additionally, there are a few longstanding genetic disorders listed by Betancur that we have excluded from the analysis because they are not genomically designated: Cornelia de Lange syndrome causes a range of physical and developmental issues and has been associated with autism since the mid-1970s, but it is genetically heterogeneous and diagnosed clinically, making it unsuitable for our analysis, which relies on genetic disorders being rigidly fixed to mutations. Similarly, phenylketonuria is a metabolic disorder that can result in a host of developmental and medical problems and was associated with autism as early as 1969. That said, it is associated with several hundred different mutations in the PAH gene as well as a small minority of cases in which PAH is normal, and so it does not meet our criteria for genomic designation. Likewise, tuberous sclerosis, characterized by nonmalignant tumors in multiple organ systems as well as developmental delay, seizures, and behavioral abnormalities, began to be associated with autism from the mid-1980s (e.g., Greenstein and Cassidy 1986; Lawlor and Maurer 1987). However, because it was linked to two different genes—TSC2 and TSC1 in 1992 and 1997 respectively—and because many cases are still diagnosed in the absence of molecular confirmation, it is similarly excluded from the data set. Of the three, only tuberous sclerosis's association with autism has been the subject of more than a handful of papers, and it is still dwarfed by the Fragile X–autism literature. Finally, the most complicated case we chose to exclude is Rett's syndrome. It is complicated not only by the fact that some cases are still diagnosed in the absence of molecular confirmation, but also because both DSM-IV (1994) and DSM-IV-TR (2000) listed Rett syndrome as a pervasive developmental disorder alongside autistic disorder and Asperger's disorder with related-but-distinct diagnostic criteria. Thus, a Rett syndrome diagnosis was considered at one and the same time as an ASD diagnosis and as mutually exclusive with other ASDs. Given these complications, an analysis of the history of Rett's syndrome and its connections to autism merits a separate paper.

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