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TRUTH AND TRUST IN STATISTICAL GENETICS

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Abstract

One of the most polarizing statements in today's public discourse is "science isn't real." To support this claim, many will cite that, in informal situations, scientists express doubts in their work or popular forms of science. To counteract these claims, scientific establishments will claim overwhelming truth and rigor to their results. Thus, today we've reached an impasse between the two totalizing perspectives. Is there a way to resolve these two perspectives? Can science be both true while disunified? Can scientists be both doubtful yet rigorous? In the following paper, I trace the development of one scientific discipline, statistical genetics, in which some researchers have expressed that their research may not be "real." With a wealth of interview and ethnographic data I illustrate a picture of science and scientists that can be both disunified and true, and the attitudes that exist within it. In doing so, I attempt to resolve the earlier questions by proposing a new way to understand scientific progress and development: disunity and distrust.

Key Terms

Statistical Genetics, Scientific Unity, Disaffection, Science and Technology Studies, Cultural Anthropology

Introduction

On a cold autumn day, I entered a hospital. The building towers over the surrounding neighborhood, its constantly lit concrete walls and helipads give it the impression of something you would find in Gotham rather than a university campus. Walking past the front desk, I pass a food court teeming with sleep-deprived medical students and physicians who forgot to pack a lunch. As I move towards my destination, hundreds of photographed faces greet me, sealed in time alongside their medical school graduating classes.

At the end of my journey, I enter a conference room. Comprising a few tables, cheap but comfortable office chairs, a large television mounted to the back wall, and a Keurig coffee maker, the room feels hollow, with multiple empty seats between each person. The presentation today focuses on a model foreign to the other researchers in the room: one on causal inference. For statistical geneticists, causal inference is one of the hottest topics in their field. Causal inference aims at identifying biological agents that *cause* a disease rather than factors *associated* with it. Many of the researchers in the room work on what they call "medically relevant traits" such as mental health disorders, diabetes, and asthma. In addition to the immense difficulty physicians have identifying biological mechanisms behind these traits, they impact millions. Thus, having a solid framework for causal inference, i.e. having a way of knowing what genetic factors *cause* diabetes would be a game changer for many of them. However, the researchers don't get their hopes up. Many have promised but failed to deliver.

Opening her slide deck, the presenter explains the goal of her model: "We have a lot of observational data so ideally we want to infer causality from this data." Moving to the next slide, the researcher stated the justification for her work. "When people propose new models for causal inference, they should have a theoretical component to compare their results to … many people just estimate without a theoretical proposition." Continuing to the next slide, she listed the terms in her model. Halfway

through describing an equation another researcher stopped her. Pointing to a term in the equation, p_i[1], he asked "but what actually *is* p_i? Or rather what is *a* p_i? Is it biologically derived? Can you give an example please?" Another researcher chimed in, "I think it might be a constant for a given population? How are you estimating it, or is it something we know?" The presenter scrolled back a few slides, showing a bunch of letters, interconnected by a flowchart of arrows. She pointed to where a " p_i" would fit between *Z, X, U, Y, O, C*. The researchers got more confused, one asked "Wait so what is *Y*?" They had initially assumed that *Y* represented the phenotype, but now they needed "an example of how [the diagram] gets from *Y* to a phenotype such as addiction," or was "*Y* the same thing as the phenotype?"

After the meeting, I chatted with a few of the other researchers who were there to sate my curiosity. I asked one, "in your own work, how did you get a statistical model by interpreting a biological phenomenon?" Smugly, she responded "I don't. The whole concept of [statistical genetics] is an abstraction. There are so many steps in between 'biology' and the phenotype we're studying ... There is a large chance that all this could be fake." Flabbergasted, I asked another researcher the same question about her work, she answered "'Anything that models reality has to simplify, but anything reflective of statistical likelihood is not 'real biology' … We also don't know if the hypothesis or even the data itself is *actually* there." Before I could stop myself, the next question fell from my lips, "So then why? Why do you continue to do it if you think it's all fake?" She shrugged, "I mean if you give me something better, I'd happily jump ship."

Reflecting on my time as a practitioner of statistical genetics, I realized that I shared the same attitude as many of my scientific peers towards my own work. While my skepticism originated in anthropological rather than scientific theory, I believed that, to some fundamental degree, my research distanced itself from "reality." And, despite my internal contradictions, I wanted to continue and even expand my work. But why? What is not "real" for these researchers and how do they determine that?

[1] Any specific equation that my interlocutors mention having worked on has been deidentified. Terms very common to most mathematical equations such as x and y have not been changed.

What is it about statistical genetics that makes it the “best option” for these researchers? And why do these researchers keep doing work that they claim is not “real”?

In recent memory, the anti-science movement in the United States has achieved unprecedented political success. One common strategy this movement employs is by leveraging a seeming disunity within the sciences: we can’t trust mainstream science because mainstream science is not unified. In response, science has crafted an image of a unified front. As a direct product of the war between these two sides is that there seem to be far fewer spaces that lie between the two. However, can science both be disunified *and* true? In this increasingly polarized environment, I believe cultural anthropology has the tools necessary to open this space.

I divide this article into five sections. In the first section I follow the prehistory of the scientific discipline known as statistical genetics (statgen) to understand the fundamental mechanisms used for generating results that their science considers “true”. In the second section, I examine some of the first papers published using contemporary statgen methodologies to understand how modern statgen creates something greater than the sum of its historic parts. Section three begins to use the framework established in sections one and two to understand how contemporary statistical geneticists come to conclusions about what is real and their dissatisfaction with these conclusions. Section four builds on section three by utilizing ethnographic and interview data to characterize how researchers resist and distance themselves from the dominant paradigms of their field. Finally, section five attempts to answer why the researchers stay in a discipline they disagree with. From this analysis, I identify a commonly overlooked mechanism for scientific unity: disaffection.

Inherited Histories

If the main tension we want to understand is a relationship to how the “real” factors into the production of statgen knowledge, then we should begin by understanding how we know something to be real in the first place. My interlocutors would often mention the value of statgen as a particular

methodology, e.g. a way of answering questions, rather than a body of fundamental scientific knowledge. What comprises this methodology? Specific moments in history mark the introduction of new ways of thinking and things to think about. By looking at the moments where statistics and genetics became scientific tools, we can better characterize the problems my interlocutors identify with statgen. Furthermore, in this process, we will open the question of how things could be different.

The popular history of the modern genetics starts with the work of Austrian intellectual Gregor Mendel. The scientific community credits Mendel as the first person to discover and characterize the base mechanisms of heredity, ushering in the new science known as genetics. While some historians of science have argued that Mendel was not a geneticist[2] in the contemporary sense, — particularly due to the distance of his work from what would become the modern synthesis of biology — this paper still places him as the "father of genetics." Mendel may not have studied genes, but he was a pioneer for his introduction of a new methodology.

Of those who argue that Mendel's *results* didn't father genetics are philosophers of science Staffan Müller-Wille and Hans-Jorg Rheinberger. Instead, they place Mendel's *methodology* as his crowning achievement. Müller-Wille and Rheinberger argue that "Mendel wanted to demonstrate that it *was possible* to elucidate structural properties at the level of hereditary dispositions, and to distinguish this level from the level of traits that manifested themselves from generation to generation" (Müller-Wille and Rheinberger 1980, 30, emphasis mine). Twentieth-century critiques of Mendel would argue that, from a mathematical perspective, Mendel's results were too good to be true. However, taking Müller-Wille's and Rheinberger's argument, we should not mistake the lack of relationship between Mendel's results and "the gene" as a lack of importance of his work.

[2] Most notably Robert Olby's piece *Mendel No Mendelian?*, arguing that "Mendel's overriding concern was with the role of hybrids in the genesis of new species … The laws of inheritance were only of concern to him in so far as they bore on his analysis of the evolutionary role of hybrids." (67)

Mendel's key intervention was not a model of how genetics worked, the term "gene" would not be used until decades after his initial experiment, but rather a proof that one *could* methodologically cobble together a connection between different levels of biological phenomenon: e.g. an overarching theoretical one (heritability) and a lower level physical one (phenotype). After the eventual rediscovery of Mendel's work, researchers, in a patchy network of Mendel-inspired experimentation, would build upon the Mendelian method. This method, "not only provided fertile ground for crossing experiments in general but also supported a Mendelian focus on controlled and analytic experimentation. This focus became the foundation of genetics, a new discipline that sought to investigate hereditary phenomena in general." (Müller-Wille and Rheinberger 1980, 33) Thus, rather than fathering in a study of genes, Mendel laid the bedrock for "genetics" as an experimental system for the study of heredity and its interwoven connections.

In the wake of Mendelian experimentation, a new field emerged combining Mendel's scientific study of heritability with the newly emerging concept of the "population": population genetics. The most notable figure of the first population geneticists was Ronald Aylmer (R.A.) Fisher who pioneered many of the foundational mathematical tools and concepts essential to modern-day statistics. One of his most significant works *The Genetical Theory of Natural Selection* combined Mendel's work on heritability with Darwin's theory of natural selection to lay the groundwork for the "modern synthesis" of evolution[3]. Furthermore, in 1930 Fisher published *The Design of Experiments*, which has been broadly cited as one a key foundation to most statistical applications in science.

Like Mendel, Fisher didn't aim to generate an entirely new theory of already established biological systems in *Design*. Instead, he wanted to prove the merits of statistics inference as a valid form of scientific knowledge production:

[3] While having a few chapters on eugenics, the current paradigm of biology would not have been possible without this work.

"I have assumed, as the experimenter always does assume, that it *is* possible to draw valid inferences from the results of experimentation … The mere fact that inductive inferences are uncertain cannot, therefore, be accepted as precluding perfectly rigorous and unequivocal inference." (Fisher 1930, 3-4)

In other words, Fisher proved it was in fact *possible* to align physical reality with statistical theory to establish a new way of verifying knowledge. By all accounts, he succeeded: in the present day, statistics has become foundational to science curriculum around the world. If a scientist doesn't perform statistical tests in their work, many will call it bad science. Thus, like genetics, statistics didn't just emerge as a set of objects we now know to be real: they are mechanisms, emerging at historic moments, that allow scientists to determine what is real.

Philosophers and historians of science have long debated how scientists and scientific communities reason about their questions. One of the more notable, and recent, individuals to take up this project was Ian Hacking. In various works, Hacking outlines a framework for understanding what he calls "scientific styles of reasoning," later adapted to just be "styles of reasoning." (Hacking 1992) Hacking argues that "objectivity," or the criteria by which we know something to be "true," is not a historically *a priori* fact. Instead, at different moments in history, new "styles of reasoning" emerge that give us both new questions that can be said to be true, and the means by which we reason them to be "true," or objective.

When a new style of reasoning arrives at the intellectual stage, so too do new objects to reason about. However, these objects are not ones we can simply observe with our senses. For Hacking, the novel objects introduced by styles come with an ontological debate about their "realness." A good example of this comes from the statistical style: the population. Does a population exist as something a scientist can discretely measure and observe? Is the "average individual" from a population real? Hacking is uninterested in answering these questions. Instead, he points out we can only begin to answer these questions by employing the style of reasoning that created them.

Scientists do not have to reason with only one style of reasoning. In fact, Hacking highlights that individuals and disciplines accumulate many styles of reasoning in their lifetimes. In one moment, a biologist can determine the relatedness of two animals based on a comparison of their characteristics according to defined categories, while at the next modeling their population's theorized gene flow over time. In this case, the biologist switches between multiple styles of reasoning depending on the object the analyze. By accumulating more styles of reasoning, we expand the possibilities of the kinds of questions we can ask. Hacking takes his point on accumulation to characterize that truths in the context of a style could not be "candidates for truth or falsehood, unless that style were in existence. The existence of the style arises from historical events … the fact that [certain questions] are candidates for being true is a consequence of a historical event." (Hacking 1985, 155) In other words, since styles arise from specific historical moments, and styles determine what can be thought of as true or false, then all objectivity and truth are historically predicated, and we must understand them in the context of specific styles of reasoning. This is not to say that nothing is true or real, instead it is to say that we cannot know anything to be true or real outside of the tools of our time.

We can now translate the projects of Fisher and Mendel into the language proposed by Hacking. Mendel, to generate truthful knowledge around the phenomenon of heritability, had to develop a new mode of experimentation to ask questions about heritability. In doing so, he generated a new way to experiment and reason about heritable phenomena. This new way of verifying knowledge is what geneticists would take into the 20th century and still utilize today. In a similar vein, Fisher introduced a new style of reasoning to the sciences through use of mathematical and statistical demonstrations. Statistical geneticists, as their name suggests, utilize both the statistical and genetic styles of reasoning to generate verifiable and replicable results. New objects of study have emerged since the days of Mendel and Fisher, such as the "transcriptome," however, as an introductory genetics course will tell you, geneticists reason about these newer objects in many of the same ways their intellectual ancestors did.

Styles of reasoning provide a useful framework for understanding how any scientific community understands reality. Perhaps a simple explanation of the sense of unreality my interlocutors feel comes from interpreting the results of their work through a different style of reasoning. After all, Hacking shows us that researchers accumulate styles of reasoning over the course of their life. While tempting, this theorization only answers part of the picture. To answer the anthropological questions of why a researcher stays doing what they call "fake" science, or why a researcher can't straightforwardly apply a different style of reasoning, we must continue following statgen's history. We must analyze the late-20th-century advancements that shaped what is now contemporary statgen.

A Moment for The Method

How does one define statgen? Often confused with population genetics, which studies the population and its relationship with its genetic underpinnings, statgen applies many theories of population genetics, but their body of work primarily focuses on elucidating the relationship between the individual and their genes. The line between the two disciplines is extremely blurry, made blurrier by many population geneticists working as statgen and vice versa depending on appointments and funding. Furthermore, geneticists often differentiate themselves depending on their organism of study. Thus, statgen further complicates the problem of classification by having its own sub-disciplines, such as the discipline of human genetics, which primarily studies humans. For the sake of simplicity, and reasons that will become clear, when I talk about statgen researchers, I primarily mean statgen researchers who do human genetics. My interlocutors, while primarily working as human geneticists, engage and identify with the broader discipline of statgen. Thus, a good distinction between population genetics and statgen might be statgen having a focus on *applied* science, meaning a translation of their findings into real world applications, particularly towards *human* health. We will be well equipped to understand this focus by understanding the technological and scientific advancements that produced it.

The late twentieth to early twenty-first centuries gave birth to numerous landmark advancements in biotechnology, with the completion of the Human Genome Project (HGP) being one of its crowning achievements. The HGP aimed to sequence the entire human genome, thereby establishing a "reference genome," which could act as a baseline for genetic mapping. In addition to giving molecular biologists the ability to further characterize human genetic character, the reference genome gave scientists the ability to describe differences between humans at an unheard scale. With the "book of life" now open for reading, it was inevitable that many would try to decipher its language.

As a biological species[4], humans share approximately 99.9% of their genetics across the board. Thus, most genetic differences between individuals and populations alike appear as small individual mutations scattered across the genome. These "single nucleotide polymorphisms" (SNPs[5]) act both as causes and markers of many diseases and traits across individuals. Thus, many geneticists would ask how well do changes/differences across a population (variance) of SNP genotypes act as markers for the variance of a phenotype? Put another way, does having a specific SNP increase your likelihood of or cause a specific disease? Once they established a baseline to vary from: the reference genome, researchers could finally put this hypothesis to the test. This was the origin of a new type of study: the genome-wide association study.

The year 2005 marked the first full scale genome-wide-association-study[6] (GWAS[7]) coming out of the journal Science. The paper described a study aiming at quantifying the statistical significance, or level of numerical association of variance, between specific SNPs and age-related macular degeneration (AMD). To do this, the researchers genotyped 44 SNPs known to be highly associated with genes thought to have some effect on AMD from past biological literature. They then calculated an empirical p-value, a

[4] An object emerging from a Linnaean classification system of reason, whose ontology is widely debated.
[5] Pronounced "snips."
[6] The true first GWAS was published in 2002 (Ozaki et. al, 2002), however it misses many of the common features of modern statgen I aim to characterize in this paper.
[7] Pronounced "G-WAS"

measure of statistical significance which gives the probability of finding their specific data within a given statistical model, and analyzed their results.

The 2005 paper shows a project only possible because of the works of Mendel and Fisher. The researchers who conducted the study demonstrate a wealth of styles of reasoning: genetic, laboratory, as well as statistical. What makes the paper particularly revolutionary was how the researchers did something different than just introducing a new style of reasoning into their repertoire: they connected multiple styles of reasoning to each other through their methodology.

A traditional genetic study would have a laboratory biologist using statistics to test data generated through the course of experimentation. If the AMD study was done a few years earlier, it might look like this: to test whether a specific gene affects AMD, the researcher must spend years mutating mice and proceeding to genotype them until they get one with AMD. If a few common mutations pop up, the researcher might then do a statistical test to determine if these mutations are commonly associated with AMD in mice. If the results are very significant, the researcher might then try to actively target the specific gene to determine its causality of AMD. However, the fact that the 2005 paper studied humans made using many of these techniques impossible.

Due to ethical issues, researchers can't mutate hundreds of human genomes to have a gene or SNP that they think causes AMD. Additionally, researchers in this case don't *a priori* know the specific SNPs they would mutate. Instead, the 2005 researchers had a variety of literature suggesting many different mechanisms and genes that *may* have a role in causing AMD. Thus, the researchers had to find a different way to reach meaningful conclusions with the styles of reasoning they had.

The GWA method doesn't just give a singular p-value, it gives the researcher the statistical significance of every SNP they choose to test. The researcher will then use population genetic and statistical theory to comb through their GWAS results. This is not to say that this approach is not rigorous or scientifically sound, quite the opposite. The 2005 researchers performed tests on "linkage equilibrium,"

they removed overrepresented variants to see if their results become more pronounced, and they restricted their analysis to more specific mutations such as analyzing one C allele rather than two. These techniques all formed a stronger link between the biological objects the geneticists wanted to analyze and the statistical reasoning they used to differentiate between them. At the end of this process, the researchers linked their biological hypothesis with the statistical results of a significant SNP: "Given the known functional interactions of genes within the RCA gene cluster ([citation] 13), variants within these genes could interact with or modify the effect of the [most significant variant]." In other words, these researchers do not simply switch between genetic and statistical reasoning, they actively construct and employ a connection between the two. This connection is what truly defines statgen as its own discipline.

In his piece *Computer Simulations and The Trading Zone*, historian of science Peter Galison outlines how, to create the hydrogen bomb, scientists produced new technologies of interdisciplinary communication. Everyone working on the hydrogen bomb wanted to avoid it blowing up at the wrong time. Thus, researchers needed a way to communicate their parts of the project effectively so that they weren't causing another researcher's part to fail miserably: would the heat generated from the chemical process affect the nuclear chain reaction leading to an undesirable explosion? Galison argues that to solve this issue, the Monte Carlo simulation emerged as a way for researchers to communicate over a shared reality in the simulation:

"But bit by bit (byte by byte), computer designers deconstructed the notion of a tool itself as the computer came to stand not for a tool, but for nature itself. In the process, discrete scientific fields were linked by strategies of practice that had previously been separated by object of inquiry. Scientists came together who previously would have lived lives apart, and a new subfield came to occupy the boundary area." (157)

In other words, Galison argues that the disconnected fields comprising the hydrogen bomb project needed "trade zones" such as the Monte Carlo simulation to function within the same workspace. Furthermore, the simulation transformed how theoretical and experimental knowledge interacted:

"They spoke an intermediate language, a kind of formalized creole: the language of computer simulations understood both by theorists and by experimenters. (It was no accident that conferences flourished with names such as "Computing as a Language of Physics.") Accordingly, the simulators became indispensable as links between high theory and the gritty details of beam physics and particle collisions." (155)

For the 2005 researchers, using only genetics to answer their question would not have generated significant results. Undergoing a statistical inquiry would have most likely left them in the realm of theory. Thus, to move forward in the scientific inquiry of AMD, the researchers did a project that effectively fused the two styles. In this new space, statistical and genetic reasoning folded into each other, inseparable and moving towards new possibilities for how to analyze biological data. The GWA method had created a new trade zone within an old object: the gene[8].

After developing this new language to talk about the gene, the 2005 researchers contextualize their results to their broader discipline:

"Plasma levels of CFH are known to decrease with smoking ([citation] 23), a known risk factor for AMD ([citation] 2). This confluence of genetic and environmental risk factors suggests an integrated etiological model of AMD involving chronic inflammation. Identification of the increased risk of AMD associated with the T1277C variant should enhance our ability to develop presymptomatic tests for AMD, possibly allowing earlier detection and better treatment of this debilitating disorder" (Haines et. al, 2005)

This conclusion places a value judgement on past biological work. The first conclusion, the suggestion of an "integrated etiological model," meaning an expansion of the biological work grounding their arguments. Hypotheses provided by previous work, that certain genes affect AMD, aligning with the

[8] For a study centered on Galison's ideas in the context of bioinformatics, see Penders, Horstman, & Vos 2008. They characterize wet-lab (biological experimentation) and dry-lab work (bioinformatics) as two different styles of research functioning around the same object. For practitioners of the wet-lab and dry-lab styles of research, who in the context of this paper, work in the same physical lab, a trade zone is necessary to share data and produce results meaningful to their respective styles. Thus, a literal and theoretical object, the gene pathway map, emerges as a shared "moist-zone," which allows "wet" and "dry" researchers to work within the same space.

paper's statistical results are ones that the authors argue to pursue, which in turn places value on past conclusions corroborated by new statistics. The second conclusion, that their identification should enhance presymptomatic tests, positions their statistical method as one that can and should guide the medicine predicated on the previous biological work. The authors place the GWA method as simultaneously useful to medicine, biology, and statistics. The researchers needed the shared language of the gene to formulate this connection.

The major turning point for GWAS' popularity occurred in 2007, when researchers conducted the first large-scale GWAS with a sample size of 5000 people (WTCCC, 2007). The study tested the significance of 7 very common medical traits such as diabetes and hypertension. Moreover, the study tested the significance of over 500,000 SNPs, making it a truly *genome-wide* association study. Like the 2005 paper, the work ends with the possibility of "translating [their] findings into improvements in human health." (WTCCC, 2007) However, the two papers significantly differ by the latter focusing mainly on its method.

The ending of the 2007 paper contains many staples of contemporary statgen. For one, it argues that their study "enables us to make several general recommendations relevant to GWA studies" and "allowed us to address another important methodological issue." The paragraphs following these quotes outline general procedures they took towards "quality control," or the exclusion and sometimes adjustment of data to reduce bias in their model. Building on their conclusion, the authors argue that their method highlights the "suitability and efficiency of the [blending of cohorts of people without the disease in data] in Britain and warrants its serious consideration elsewhere." In other words, instead of making a case for the usage of a general statistical style of reasoning for biological work, the authors argue for the continued use of the GWA methodology to generate biologically meaningful knowledge.

The GWA methodology was and is not without its flaws. A lasting issue in both 2005 and 2007 papers is the problem of population structure: where both genetic and phenotyping variance are highly explained by patterns in human assortment over time. The 2007 paper argues that with the right

procedures and assumptions, problems such as these can be corrected for and combatted. My own research studied this problem: a project trying to find harder to detect population structure in GWAS. The focus on the value of GWA methodologies in biological and medical studies is inseparable from the wider ideology of contemporary statgen.

Since the 2007 paper, the usage of GWA methods and results has become commonplace throughout biological disciplines. Papers started using "GWAS" as a plural term rather than just citing an individual "GWA study." As of writing, the main GWAS catalog lists over 86,000 studies with published GWAS summary statistics[9]. Thus, instead of publishing more GWAS using the same models, a new kind of researcher entered the scene: the methods developer. In these "methods development labs", researchers attempt to improve existing methods and create new types of statistical models for GWAS.

The trade zone at the center of statgen highlights a different process at work rather than a Hacking-esque employment of a variety of styles of reasoning. With the gene as an object of study, the line between the styles of reasoning employed by the statistical geneticist blurs: a population says something about a gene pathway, and both have implications to public health. In recent years, some methods development labs and researchers have shifted away from corroborating and generating biological hypotheses. In the case of my interlocutors, they look into the realm of prediction.

Math In Action

Now that we have a better idea of what statgen *is*, we will examine the common practices contemporary statistical geneticists *do*. Only by characterizing some of the common practices in the field can we understand the critiques my interlocutors have with them. Furthermore, these practices highlight in less abstract terms how these researchers work within the context of styles of reasoning and trade zones.

[9] I sourced this number from https://www.ebi.ac.uk/gwas/downloads/summary-statistics. Most likely the number has increased since writing.

The most common point of contention my interlocutors expressed with their work was prediction. The main form of prediction GWAS results take is polygenic risk scores (PRS). GWAS generate immense amounts of summary statistics. The main statistic GWAS use to generate results is the p-value, which researchers use to identify statistically significant SNPs. PRS use another statistic, the β estimate, to estimate the "effect size" of the SNP's presence on the phenotype. To understand how PRS work and, more importantly, how researchers think about PRS, we need to understand how researchers represent biological data.

Statistical geneticists do not store genetic data in test tubes. In the wake of the 2007 paper, both smaller-scale to national biobanks consisting of many kinds of phenotypic and biological data emerged. Biobanks generally come through medical contexts, where researchers can ask participants if they want to have their genome sequenced. Some biobanks, like the UK Biobank, contain vast amounts of phenotypic and genotypic data. In the UK Biobank's case, it has data from over 500,000 individuals. Researchers from across the globe can apply to access those data. Companies such as 23AndMe have biobanks, which generally people opt into. Finally, some researchers work on biobanks funded by the U.S. government such as the Million Veterans Program which comprises, well, over a million veterans.

Fundamentally, computers represent SNPs and disease in data with 0's and 1's. If a patient has the disease of interest, the researcher represents their phenotype as a 1 and vice versa if they are negative for the disease. SNPs function the same way: 0 for a homozygote of the most common allele in the population, 1 for a heterozygote between the major (most common) and minor (less common) allele, and 2 for a homozygote of the minor allele[10]. The GWA method will then attempt to quantify how good of an indicator having a higher number for a SNP is for having a 1 in the disease of interest. Additionally, the GWA method will calculate β, or the "effect estimate," for each SNP, which estimates the average increase (or decrease) in the disease number based the change in the numerical representation of the SNP.

[10] Technically speaking it's represented in 2 bits of binary data: 00 (0) for homozygous major, 10 (2) for heterozygote, 11 (3) for homozygous minor, and 01 (1) for a missing genotype. https://www.cog-genomics.org/plink/1.9/formats

In mathematical terms, for each SNP, the GWA method calculates an equation like the following: $total\ effect\ of\ SNP_i\ on\ trait = SNP_i \times \beta_i$. Once the researcher calculates β for every SNP of interest, they can plug all these estimates together to make the following model:

$$Phenotype_i = \beta_1 SNP_1 + \beta_2 SNP_2 + \cdots + \beta_n SNP_n + Error_i$$

This is what researchers call "the additive model,"[11] which, as the name suggests, assumes polygenic phenotypes to be the summation of the presence of many small effects from many SNPs. A key term in the equation is the "error" term. The error represents any variance in the phenotype that can't be explained by the genetic variance. In a mathematical sense, this term is a numerical constant that represents the baseline number for the trait. Researchers often refer to this term as the "environment," as it represents any other unmeasured factor that contributes to an individual having a trait. A common way of talking about this is by saying something like "genetics explains 24% of the variance in this trait and the environment explains the other 76%."

The idea of variance explained by genetics, which they refer to as the "heritability" of the trait, reveals a mechanism on how the trade zone of the gene functions in the modern day. When talking about heritability, biological reasoning guides statistical research and vice versa. If researchers "know" that a trait is biological in character, and a model for that trait has a very low heritability, then something must be wrong about the model as it's not capturing a relationship the researchers know to be true. Researchers call this phenomenon "missing heritability," which refers to heritability that their models fail to capture but exists elsewhere. On the other hand, if a model has high heritability for a previously thought to be non-biological trait, assuming the model doesn't have biases leading to this result, then the researchers may be inclined to look for biological causes for the trait. One trait which has high heritability in some

[11] R.A. Fisher first proposed the additive model.

studies, educational attainment[12], still has very impassioned statgen critics and supporters of its biological character[13].

Researchers can use models such as the above one for prediction. However, it is very hard to reach highly interpretable conclusions with a binary phenotype. For instance, let's take a model for Alzheimer's trained on a biobank mainly composed of older patients diagnosed with Alzheimer's. Once a computer finishes running the model, it generates a β estimate for each SNP that we could then multiply my genotypes by. If SNP rs871269[14] has a β estimate of 0.00078192 and I have a 2 for that SNP, then the "estimated genetic contribution" of rs871269 would be $0.00078192 \times 2 = 0.00156384$[15]. The model would then repeat this on every SNP effect estimate until it summed all the terms. At the end of this process, there is pretty much a 100% chance that my numerical "score" for Alzheimer's won't be a 0 or 1. Instead, the model will most likely pop out an unintelligible decimal such as 0.5778901. This is one reason why researchers add "risk" to the language of some PRS, as "scores" like this work better at predicting one's risk or predisposition to a disease, rather than whether they have the disease.[16]

One benefit of the overwhelming amount of GWAS summary statistics that are publicly available is that some methods development researchers don't need to conduct their own GWAS[17]. A summary statistics file normally looks like the following:

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[12] Biobanks may represent educational attainment in many ways such as years spent in school, test scores, highest degree obtained, etc.

[13] Notably, many critics of educational attainment due so based on the models that achieve high heritability are still wrong: a correct model is one that still reinforces what they know to be true biologically.

[14] One of the "lead variants" found by Wightman et. al 2021

[15] If I had a "0" for that SNP instead, then the SNP would have no genetic contribution to my phenotype as the term would cancel out.

[16] Some PRS are already gaining traction and usage in *in vitro* fertilization to select for embryos with particularly low or high PRS for certain disorders (Turley et. al, 2021) and arguments for their use in clinical settings for disease prevention and risk are becoming more commonplace. Furthermore, a recent study explored the possible consequences and benefits of "heritable polygenic editing" (HPE) where GWAS results could be used to identify targets for genetic editing. While the paper argues that HPE could lead to a new wave of eugenics and openly condemns HPE's usage for eugenic purposes, the paper still proposes that, with the right precautions, HPE "can be distinguished from past eugenic practices, as in contemporary clinical genetics."

[17] Most computers cannot run analysis of the size of a GWAS so they require the assistance of high-performance computing, which generally take the form of computing centers that researchers can log into remotely. Once granted access, researchers will download the genotype and phenotype data onto a high-performance machine. Furthermore,

Name	chromosome	base_pair_location	other_allele	effect_allele	Trait	Cohort	Model	odds_ratio	ci_lower	ci_upper	p_value	effect_allele_frequency	standard_error
SAMD11(ENSG00000187634).GENE.M1.0001	1	925941	ref	M1.0001	Phe10_J450__BIN	UKB_Freeze_450_EUR	ADD-WGR-FIRTH	0.362407	0.025232	5.20524	0.455326	0.000301601	1.35954
SAMD11(ENSG00000187634).GENE.M1.001	1	925941	ref	M1.001	Phe10_J450__BIN	UKB_Freeze_450_EUR	ADD-WGR-FIRTH	0.706826	0.142073	3.51653	0.671673	0.000812002	0.81861
SAMD11(ENSG00000187634).GENE.M1.01	1	925941	ref	M1.01	Phe10_J450__BIN	UKB_Freeze_450_EUR	ADD-WGR-FIRTH	0.970725	0.315815	2.98373	0.958639	0.00179543	0.572911
SAMD11(ENSG00000187634).GENE.M1.1	1	925941	ref	M1.1	Phe10_J450__BIN	UKB_Freeze_450_EUR	ADD-WGR-FIRTH	0.861817	0.468166	1.58646	0.632899	0.007473	0.311342

Figure 1. Publicly available summary statistics file of asthma from Buckman et. al 2021

with the different statistics as columns. Since this file contains *all* genotyped SNPs on the genome, researchers will filter out SNPs outside of a certain "significance threshold." This means only including SNPs in the PRS that have a p-value under a certain value: the standard axiom is the lower the threshold the less biased, but higher thresholds tend to have more statistical "power." The definition of a "good" significance threshold tends to vary between studies. Researchers will often define the "best" significance threshold as the one that maximizes the prediction accuracy in testing data.[18]

Moving back to the conference room filled with methods development researchers, we now can better characterize the research practices that played out. The researchers in the room "know" that there is a causal effect connecting the genotype to phenotype, but they don't know the specific mechanisms by which to determine said causal relationship. By creating and testing equations, they attempt to establish links between gene and phenotype. They propose new ways to theorize the connection between a variety of points including, but not limited to data, equations, genes, biobanks, populations, summary statistics, and polygenic scores.

The process of assembling a new theory of biological connection resembles something akin to an inverse version of what Bruno Latour characterizes as "circulating reference." By reference, Latour means the process by which researchers take samples and eventually leave the "field" behind, producing a chain of reference points which they can use to carefully trace back to the original generator of said sample. Many statistical geneticists, including my interlocutors, don't go out into a field/lab, collect data,

running large GWAS can take days to weeks to finish computing, so much of the research cycle of a statgen researcher revolves around waiting for your computer script to finish running. Thus, most of the work and actual *research* for a methods developer comes from proposing statistical models and then evaluating how well it works through the above pipeline.

[18] A very good tutorial on how to run a PRS can be found from the documentation of the PRSice software: https://choishingwan.github.io/PRSice/step_by_step/

and produce reference points to trace back to the individuals they originally genotyped and phenotyped[19]. Additionally, much of the data used for GWAS is de-identified, meaning the link between data and the individual is rendered somewhat invisible. Thus, the research done by my interlocutors takes two already created "references" of the population: the genotype and phenotype, and tries to characterize the mechanism connecting the two, which, they assume, exists in the original sample.

Latour takes interest primarily in using the concept of circulating reference to understand how soil scientists link back the various representations of soil to the original field where they collected it. The soil scientist knows each reference at every step of the process because they created them. On the other hand, many methods developers focus on already made references: the various types of data. As one researcher put it:

"[A more mathematically oriented researcher] tries to find a certain gene or SNP near what we know to be a gene that is 'real' in a biological sense. Then he tries to find a direct relation physically to a gene close by: e.g. this SNP associated with height in a GWA study is physically [in linear unfolded space] close to a growth hormone receptor and then they say that this SNP causes height. But they completely ignore how biology works, like the fact that DNA folds"

This notion of ignorance highlights that statgen does not have a uniform spread of knowledge about statistical tools and biological paradigms between researchers. DNA sequencing currently works by effectively laying out the whole chromosome and reading each nucleotide in a linear fashion. Researchers who have worked with DNA sequencing or combed through additional literature know that DNA twists and turns in 3-dimensional space, which produces relationships and closeness between two areas on the genome that are linearly far apart.

My interlocutors took issue with the type of understanding researchers like the above employ. They believe the way that many "mathematical" researchers attempt to reverse engineer through

[19] There are major exceptions to this where some researchers conduct clinical studies, collect their own data, and engage with the communities whose data they research.

imperfect, or even incorrect, reference points to “get back to biology” is extremely wrong. Many told me that this way of thinking flat out ignores “how biology works.” Yet, for some, even when thinking very heavily about biology, this process can have the exact opposite effect from their intentions and even exacerbate harm.

When I asked Robert, a PI, why some people leave statgen, he answered stating that “many people are motivated by what they *thought* statgen was. Their values don’t change while in statgen, but their perception of it does.” One grad student, Susan, still in statgen said that before entering science she “was taught about Rutherford's experiment and thought *that’s so clean and cool*. When I started in bio[logy], I thought I shouldn’t settle for an unclean science.” However, after being in statgen and science for a few years, her outlook changed:

“Things also get tricky when you do or read work that you believe is good but point in the opposite direction of your prior beliefs (maybe you find ancestry differences that you wanted to show weren't real, or maybe your results are that education[al attainment] prs gives you significant results) and you need to weigh your beliefs as a scientist against your beliefs as a person. This is why I found this way of looking at science was not really for me. In my current work, where I do methods, it feels more like I'm studying the way people do biology rather than doing it myself. In a way, by making my work less translational, it made it less personal. Where my previous work was directly trying to help the lives of patients or specific people, my current work is trying to help the work of other scientists and that's where I try and find meaning. I guess you could say that by spending more time thinking about what other people in the field care about, need, or might be doing wrong, my work becomes more useful and therefore more ‘real’ and that feels like a more achievable goal than what I was aiming for before”

In her attempts to find the relationship between the points on the chain of reference, Susan ended up affirming a reality that she fundamentally disagreed with. In fact, she believes that showing that an educational attainment PRS gives significant results could cause harm to real people. Over time, Susan accumulated enough of these disconnections between the reality reinforced by her work and the one she knew to be true. While many might have left statgen in her place, she stayed by focusing on making sure the work of others doesn’t perpetrate harm. In Susan’s case, even if the modeling work of mathematical researchers in statgen isn’t real, her work that improves or disproves it is.

We now have outlined a general picture of the underlying mechanisms that create a sense of realness within the scientific discipline of statgen. Statgen's trade zone, the gene, binds together the two main styles of reasoning present in the discipline: genetics and statistics. Starting with one or the other, the researcher attempts to strengthen the relationship between the styles through crafting and applying models that, to some extent, use both. A better model betters biology and statistics, and it can have medical applications. Thus, a researcher can do further work on already established abstract methods to improve them and make them more real. One way that the sense of statgen not being real arises from is an interruption of this process: a bad model or bad reasoning means a model less connected to reality. However, some of my interlocutors find their work to be not real due to factors completely outside this process.

Innovation or Error?

Sitting down in the corner of a dimly lit coffee shop I wait for today's interviewee. Kate has worked as a statgen researcher for many years and openly talks about her frustrations with the discipline. Today she agreed to talk about how she got into statgen.

"I initially trained in biology, doing my bachelor's in it. I didn't really know what I wanted, but thought I wanted to be a physician. But I realized that I didn't care about the science I was doing in 'raw' biology … I wanted to connect with people and groups exhibiting diversity. I wanted to think about people in a *useful* way"

Kate's entry into statgen is not an unorthodox one. I interviewed grad students and principal investigators (PIs) across three methods development labs, and none of them concentrated in genetics in undergrad, some didn't even study biology. Instead, they studied one of statgen's neighboring disciplines, some of which are broader biology, computer science, mathematics, and statistics.

Kate didn't start working in statgen until grad school, which she didn't foresee as what she would pursue. Once she started studying statgen, she realized how many problems the field faced. Kate has many issues with the ways statistical geneticists employ their assumptions and models:

"[mathematical models are] not capturing all of reality … Artificial boundaries are placed on *who* gets kept in data. Many people [are] missing because there is already a purposeful conclusion trying to be made … People get excluded from data due to [them being] 'bad samples' or [having] some 'missing data' etc."

Kate believes that the root of these issues lies in problems with diversity. This takes the form of statgen being most influenced by people who fall broadly into the category of "cis[gender] het[erosexual] white men," and the field "abstracting away from the people of here and now" in their models and data. So, motivated by these issues, she decided to do research that exemplifies diversity.

Kate's primary project centers around what researchers call a "gene by environment" model or GxE. Kate assumes that "environments shape people and that your lived experience translates somehow into your health." So, working with that idea, she builds and refines GxE models. One version of a GxE model could look like this:

$$Phen_i = \beta_1 SNP_1 + SNP_1 * (Environment)_i + \cdots + error_i$$

This equation models SNPs as having a "genetic" and "environmental" contribution to the phenotype. In other words, the presence of the SNP still has a β from the additive part, but the SNP may also have some other numerical contribution to the phenotype depending on whether the individual has had exposure to some environmental condition, such as their zip code being within 10 miles of a power plant. Biobanks represent environments and phenotypes as the same thing: i.e. numbers. A researcher could build a GWAS or PRS on the level of urban traffic you've been exposed to or incorporate said exposure into the model. There is no fundamental difference between defining a term as a phenotype vs environment, as biobanks store them both as numbers and they both will function as numeric predictors.

Some example "phenotypes" include one's BMI, height, disease status, and "baked bean intake."[20] Some example "environments" might include one's sex[21], exposure to nitrogen oxide, and zip code.

In addition to GxE models, researchers can make their models more complex in numerous ways. One example of this is epistasis, or nonlinear gene interaction, which is central to many researchers' work. Researchers have known about "non additive variance," or variance that defies the assumptions of the additive model, as a possible contributor to the "genetic architecture" of the trait, e.g. the underlying biological mechanisms, for a very long time. One example incorporating nonadditive terms could be a model such as the following from Smith et. al 2024:

$$phen_i = b_0 + X\beta + W\theta + \epsilon$$

Where they model a phenotype as a summation of a constant, b_0, an additive term, $X\beta$, and an interaction (nonlinear) term, $W\theta$. Generally, these papers aim to improve the accuracy of prediction based on genotypes. One researcher explained to me that "we *know* that biology doesn't work like the additive model at the fundamental level. So, biologically informed models *should* work better overall." (emphasis mine). Thus, knowing that their models aren't real doesn't stop them from making models that get closer to "real" biology.

In addition to an environment term, Kate and Sam, a PI I interviewed, both try to incorporate "lived experience" into how they do their research and, to a limited degree, their models. Kate worked on a paper in which, depending on the results, there would be broad political implications to the community involved. They found that with current genetic technology and data, they couldn't reach results that would be helpful to the community involved: "We had to take this very seriously, which radically changed how we wrote. This led to us ending up in an anthropology journal rather than a genetics one." However, this paper didn't have any impact in statgen as "people don't read across disciplines." When Sam tried publishing a discovery GWAS in individuals with extremely different genetic ancestries, peer reviewers

[20] Yes, this is real: https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=10400

[21] Since we "know" the genetic causes of binarized biological sex, researchers treat sex as more of an environmental category as one will have biological effects from being on sex or another, such as hormone levels, and social effects that may lead to changes in biological phenotype. Another example that falls into this category would be age.

would often ask them to split up the individuals into different ancestry groups to "draw statistically meaningful results."[22] Sam said that it was not uncommon for "reviewers to not trust [the work] scientifically even if they agree with it personally." These two examples show that statgen researchers seemingly do not have a desire to work with the objects produced from non-scientific forms of reasoning and knowing. In other words, while they may read and think across disciplines, they do not do the same for nonscientific styles of reasoning.

I'm inclined to define the opposite position to Kate and Sam as what Thomas Kuhn defines in *The Structure of Scientific Revolutions* as "normal science". For Kuhn, once a scientific paradigm achieves stability, the science that works within it functions effectively to "puzzle solve" the questions that the paradigm determines. Not unlike a style of reasoning, a paradigm outlines a set of questions that a scientific establishment can ask of the world with a certain set of means. During the paradigm's lifespan, scientists working from the paradigm encounter objects and questions that destabilize it. Sometimes scientists solve these "anomalies," however at a certain point the paradigm accumulates a critical mass of them such that the paradigm must reconstruct itself. Kuhn argues that in these moments, scientific revolutions occur.

Many of the questions answered by the normal science of statgen I've already outlined: those concerning missing heritability, nonlinear methods, and other types of biological data. A more peripheral example of statgen's normal science came from Robert, a PI: "the most inspiring people in statgen aren't thinking about math at all: they're always thinking about biology. Most of the math in statgen is relatively simple: it comes easy when you have a very good understanding of biology … there are a lot of people trying to understand *what* a gene is." Susan described the attitude of the statgen paradigm by simply stating that "you need both biology and mathematics to understand the world."

According to Sam and Kate, incorporating "lived experience" and "diversity" into statgen models is something fundamentally different than making biologically or environmentally informed models.

[22] This is very common statistical practice: training datasets often are of one genetic ancestry, and testing samples are all other ancestries.

What they might want, then, would be something resembling a scientific revolution. Kate argues that "there is an elitist idea of real/hard science that … only see value in [lived experience] when it's *proven."* Sam believes that "We're not the experts on an individual's experience, but we can offer a perspective from a genetics background." As we've seen, in a standard GWAS, researchers perform numerous statistical tests and procedures to determine whether their model works. However, as Kate points out, one cannot mathematically prove with ease, if at all, other truths stemming from sources such as familial stories and oral histories. Refashioning the entire apparatus of statgen to reorient it around assumptions that don't exclude diverse individuals and incorporate lived experience would be a herculean task. Additionally, Kuhn would be skeptical of one's capacity to force an entire scientific revolution on their own.

For a scientific revolution to occur, a paradigm needs unexplainable anomalies. Paradigms shifts become necessary when the paradigm accumulates enough of these small anomalies or encounters one too large to ignore. While unexplainable by contemporary statgen, the broader paradigm does not consider lived experience and diversity anomalies. It's one thing to say that a singular anomaly doesn't contradict an entire paradigm, but it's entirely different to not acknowledge something as an anomaly in the first place. Thus, Sam and Kate work to prove that lived experience and diversity are, first and foremost, anomalies within statgen's paradigm. They conduct "anomaly work."

By trying to connect nonscientific forms of evidence and reasoning to statgen, Kate and Sam aim to introduce them as anomalies into the statgen paradigm. In doing so, they push against the limits of what the statgen paradigm considers an anomaly and a valid path of scientific inquiry. The constitutive trade zone and styles of reasoning don't just determine how researchers come to conclusions: they limit the possibilities of what can be classified as an anomaly of study. These "borders of reasoning," as I call them, are what researchers such as Kate and Sam push up against in their search for something better. The borders give statgen analytical power and a consistent category of reality while enclosing it off from other possible anomalies.

One may argue that statgen is already at the early stages of a scientific revolution. Some researchers are currently interested in epigenes, or biologically heritable traits that don't stem from genes. Additionally, the gene may be slowly losing its place as the center building block of life as objects such as the transcriptome, single cell data, or the proteome, disrupt our understanding of the gene central to many phenotypes. All these biological data were anomalies or problems to be incorporated or solved by statgen from the get-go. Until statgen considers lived experience and diversity as anomalies, any scientific revolution that happens will not include them in the resulting paradigm.

I am not necessarily arguing for a complete transformation of statgen such that lived experience and diversity become central questions for statgen to "puzzle solve" through normal science. Rather, I want to bring attention to the fact that discussions of scientific progress often ignore the anomaly work that Kate and Sam conduct. In analysis of paradigms, we often focus on anomalies that already exist in the scientific discipline. Kate and Sam show that there may be individuals who do the work of finding anomalies, grappling with them in the context of their discipline, and who try to establish them as anomalies to be grappled with by their scientific discipline more broadly, all while experiencing pushback from their scientific peers. Maybe nothing will come from Kate and Sam's anomaly work, however others will inevitably come and try to do the same. Regardless of their success, science and technology studies should take note of this work.

This analysis, for the most part, answers my questions on what researchers perceive to be so "fake" about statgen research even when it is rigorous. Statgen, and science more broadly, is a rigid object with a set of mechanisms that keep a sense of reality contained within its borders: when one leaves its borders or comes from a place outside, the stability of that reality disappears. We now remain with one question: why do they stay?

Other Statgen

Philosophers and historians of science often ask the question of "is science unified or disunified?" Galison introduced the concept of trade zones to understand the ways in which disciplines can become

more unified from necessity. While trade zones can describe the work of the statistical geneticist, we cannot use them to characterize the inner tensions of the scientists actively working on reinforcing them. Trade zones cannot explain why the researchers who told me they "want to burn down statgen," stay and have become PIs. It is very easy to dismiss this attitude as what philosopher Slavoj Žižek calls an "ideology of cynicism," whereby "they know very well what they are doing, but still, they are doing it" (Žižek 1989, 28), however I believe that something different is at play.

According to my interlocutors, the passion for strengthening trade zones, normal science, and anomaly work is not uniform or even shared across the majority of statgen. Robert jokingly told me that at conferences he only hangs out with "the 4 or 5 nerds who are actually interested in doing biology and helping people." While desiring to "do good," Kate, Sam, and Susan all expressed dissatisfaction with the trade zone strengthening work of statgen. Yet, they continue to build state-of-the-art GWAS and PRS. Perhaps they don't stay for the work, but instead because of the relationships they have with their peers and broader statgen.

The core question that sociologist Richard Sennett grapples with in his book *Authority*, is what the core binding forces of society are. As the title of his book suggests, he uses authority as the primary case study for his project. The traditional view of authority Sennett works with are types of authority laid out by Max Weber. Weber argued that people interact with authority primarily through alignment: one submits to authority when they agree with the source of said authority: tradition, legality, or charisma. Sennett points out that this view of authority primarily relies on a conflation of authority with legitimacy: "People will not obey, [Weber] believes, those they think are illegitimate. The consequence, to Weber, is that we can always tell when a sense of authority exists in a society: it is when people voluntarily obey their rulers. If they have to be coerced, it is because they don't find the rulers legitimate." (Sennett 1980, 22). In other words, Sennett argues that Weber believes that authority binds societies together in a *positive* way: when people align with the source of authority, social bonds are reinforced, when others disagree,

revolutions occur[23]. Sennett proceeds to highlight cases where positive authority does not make up the whole picture.

Sennett first analyzes a woman's relationship with her parents. In this example, a woman got into a fight with her parents over a suggestion to move out of the city after a particularly bad break up with a man whom her parents disapproved of. This situation was not new: many relationships with men her parents disapproved of had come and gone, in fact she described this as a form of rebellion against her parents power over her. What caused her to be particularly averse to her parents in the most recent breakup, then, was not their disapproval of the man she was seeing, but that they suggested that she move away. In a Weberian analysis of the authority, one would argue that her disobedience is a direct consequence of her parent's a lack of authority. However, Sennett points out that she still acknowledges and works within the bounds of her parents' authority.

During relationships her parents disapproved of, the woman would regularly spend weekends with her parents: allowing them to take care of her emotionally and physically. When she dated men they approved of, this activity stopped. Sennett states that "It is during her periods of disobedience that she lets them take care of her on weekends; defiance erects a barrier which makes her feel safe enough to taste the pleasures of dependence. To say she is rebelling against authority is a mistake; she is rebelling 'within' authority ... She disobeys, but they regulate the terms." (31). In other words, the woman needs to rebel against the authority of her parents in order to accept its power over her. Within this model of authority, "dependence and transgression are inseparable." (33).

With the push for prediction in clinical settings and the suggestion of polygenic editing, the capacity of statgen to do harm is alarmingly real. Many of my interlocutors mentioned themselves or their family having negative experiences with medicine as a reason for wanting to go into applied science. While starting off optimistic of statgen's capacity to do good, they now find themselves disillusioned with science more broadly. They described their work as a direct response to the broader discipline of statgen.

[23] Not to be confused with the scientific revolutions mentioned earlier in this piece. Weber means material revolution.

Kate, pessimistically, stated that "I mainly tell people *not* to use models rather than how." Sam stated that they do their work partially because others refuse to. In other words, Kate and Sam's work is not solely for the sake of doing good science: their work is a response to the science they disagree with.

To further his point, Sennett analyzes the attitude of accountants towards their boss. Here, accountants hate their boss, frequently coming in absent and resisting work orders as much as possible. However, when they do work, they work hard and well. When Sennett suggested to the accountants that they just move to a section of the company with easier work and a better boss, which they could do, they rejected his proposal vehemently. One accountant commented on this response stating, "They need her … they don't like her and they're not lazy, but they need her to give the work a point." (35). Sennett argues that this attitude comes from the particular relationship the accountants have with the authority of the boss. They derive meaning from the authority and failures of the boss, "They use the boss as a negative model; whatever she is and she does, the opposite is what they want. … a real, creditable authority is the opposite of whatever you are." (35). In other words, a *negative* authority acts in this case: meaning and acceptance of the authority only come through rejection of those who exercise it.

On the other side of the spectrum of my interlocutors, lie those who believe that good can still come from statgen. However, their work isn't just good in isolation, it's good because the work of others exacerbates harm. Robert, the most optimistic of my interlocutors, believes quite strongly that a majority of statgen researchers aren't interested in helping people. Thus, his work is even more important than contributing to basic knowledge: it fights the harm done by other researchers. Susan, on the less negative end, told me that "[other researchers] are going to [research] anyway and I believe that people should be doing it right. Regardless of morals, if we're doing it wrong it's a huge waste of money." In other words, a primary reason my interlocutors stay in statgen is by forming and maintaining a particular, often adversarial, relationship to the broader authority of the discipline.

We now can answer the remaining questions posed at the beginning of the piece: what makes statgen the "best" option for the researchers? And why do they stay? For some, it's simply statgen's power to utilize their already developed styles of reasoning to generate applicable knowledge. However,

for others, they find meaning in rejecting the authority employed by conventional statgen. Put in Sennett's terms, many researchers don't rebel against the authority of statgen and science, they rebel *within* their authority.

While all my interlocutors expressed different relationships to the authority exercised by statgen, the representative of the authority was always the same: "the rest of the field." It is this "Other Statgen" that my interlocutors orient themselves against. Other Statgen does not care about helping people. Other Statgen generalizes, it solves mathematical problems and expands them to less specific contexts. Other Statgen does not care about diversity or lived experience. Other Statgen is composed of people looking for tenure or an industry job. Other Statgen is not interested in what I define to be *real*. Regardless of how polarized the two sides are, my interlocutors and Other Statgen comprise two parts of a greater whole in their scientific discipline.

My point here is not to argue for a radical dissolution of statgen due to its disunity. Rather, I hope that I have highlighted that what binds together researchers in a scientific space does not have to be fascination and dedication to their subject. Rather, as philosophers and other anthropologists have pointed out, social relationships and perceptions maintain what we know as science. In the case of statgen, I do not know whether the dismantlement of Other Statgen or a reckoning with science's value systems would lead to a radical transformation of science. However, I do know that statgen has authority without legitimacy: it is a science held together by its very disaffections.

Concluding Thoughts

In this paper I have sought to answer two primary questions. The first comes out trying to understand a common sentiment from my interlocutors that their research isn't "real" in one sense or another. The second asks why these researchers keep doing their research when they have this sentiment. To answer the first question, I traced the history of statgen from the genetic experiments of Mendel to the modern-day predictive algorithms constructed in methods development labs. In doing so, I showed the various methods of scientific reasoning and technologies of interstylistic communication employed by

statgen to produce robust scientific knowledge that can be considered "real." Following this, I characterize how the previously mentioned methods and technologies create disciplinary borders that my interlocutors push up against, thereby creating a disconnection between what the researcher knows to be real and what the discipline can reason to be real. In answering the second question, I highlight one of the social mechanisms that makes statgen the "best option" for my interlocutors: rejection.

I worry that readers may come out of this paper with a sentiment resembling "this *proves* that science isn't real: the scientists don't even believe what they're doing!" This is the complete opposite conclusion to what I'm arguing. By characterizing science and reasoning as historical processes, we come to know what questions we can ask and what truths we can learn. Furthermore, it prepares us for when we eventually encounter the limits of what a specific style of reasoning can provide. Hacking, quoting Chomsky, states "We know she might cease to cater to our interests, but at present (says Chomsky) we have no alternative to a Galilean style …if we want to engage in certain pursuits … we must reason with our reasons. Other styles of reasoning may occur; some are current. Other people may have other interests." (Hacking 1985, 164) Every scientific discipline has the way they ask questions that they can reason about. Understanding reasoning as historically contingent does not make its conclusions any less true, instead it opens a conversation on what limits and objects we may be avoiding. In many cases there are no alternatives to the styles of reasoning we employ at this moment, however this does not mean a new style of reasoning may develop. Statgen's styles of reasoning may be the "best option," however they only hold this position for now.

The second part of my strawman argument involves the doubt of the researcher. Nowhere in this piece do I say that my interlocutors do bad science. In fact, their doubt and disillusionment make them better scientists: some of my interlocutors mentioned that they actively cultivate internal doubt in their results to not accept results that are "too good to be true." I hope to show that scientists can be motivated to do good science not out of belief in their discipline, but a complete disaffection with it. Good science and good scientists do not have to come out of passion. Doubt, disunity, and disaffection produce truth and "good" science just as well as their counterparts.

Another thing I worry may come out of reading this piece is a perception that I have crafted a manifesto arguing that we should strive for a "true" form of rationality that incorporates every style of reasoning within its borders. When it comes to something like this, I'm inclined to agree with Hacking: there is value in the disunity of the sciences. Hacking warns against an "imperial kind of rationalism" (Hacking 1985, 164), whereby we pave over all individual rationalisms for what is perceived as the "true way of thinking about the world." I do not want to live in a world where everyone thinks the same, and I think my interlocutors share that desire. If we establish a homogenous way of thinking, then what new questions can humanity ask about the world? What new possibilities can we hope to bring into being?

As I write this piece, the scientific establishment of America is undergoing radical changes in both material and political economy. Earlier this year, The Trump Administration froze billions in federal funding to research-institutions across the country. When this happened, scientists fell into disarray: voicing their opinions on twitter and attending protests. However, when the dust settles and the post-DEI era of grants emerges, what will these new relationships between individuals, disciplines, and institutions be like? As underfunded and further disillusioned scientists leave the scene or make the choice to remain, how will the internal and public perceptions of science change? Will science become more unified? Will science lose more authority? Only time will tell, but I believe cultural anthropology has a place telling that story.

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