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The chromosome 22q11.2 deletion: From the unification of biomedical fields to a new kind of genetic condition

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ABSTRACT

How can genetics reshape nosology? This paper examines the way knowledge about a genetic mutation – the microdeletion at chromosomal locus 22q11.2 – transformed our understanding of several rare clinical syndromes and designated a qualitatively new population of patients. Taking the 1400 papers about the 22q11.2 deletion and the clinical conditions with which it was associated, we generate a network of papers tied by citations for each of the last 35 years. Using a modularity algorithm, we identify communities and evaluate their salience for the networks' overall structure. This analysis, supplemented by historical research and fieldwork with relevant experts and the advocates of affected children conducted during 2011–12, reveals that the 22q11.2 deletion acted as a 'boundary object' that unified clinical literatures and led to the emergence of a new kind of medical condition: 22q11.2 Deletion Syndrome (DS). The case of 22q11.2DS extends our understanding of 'genomic designation' – the delineation and diagnosis of clinically diffuse conditions according to characteristics of the genome – and demonstrates that observations from genetics can reconfigure existing categories of biomedical research and lead to the emergence of qualitatively new diagnostic categories.

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Introduction

What does it mean when someone has a microdeletion of genetic material at site 11.2 on the long arm of the twenty-second chromosome? Today it means they have 22q11.2 Deletion Syndrome, the second most common genetic disorder after Down syndrome (Bassett et al., 2011). It means that they and their family have entrée into a growing network comprised of biomedical research, clinical treatment, support and advocacy headlined by the International 22q11.2 Deletion Syndrome Foundation. It is a diagnosis that is thought to explain and encompass most of the incidence of older diagnoses like DiGeorge Syndrome and Velo-cardio-facial Syndrome (VCFS) as well as some cases of conditions ranging from schizophrenia and autism to constipation, malar flatness and hypocalcaemia. 22q11.2 Deletion Syndrome (22q11.2DS) can cause severe congenital heart defects and developmental delay or such a mild phenotype that the patient will not seek medical attention well into adulthood, or perhaps never at all (McDonald-McGinn et al., 2001). Finally, finding the microdeletion at 22q11.2 is increasingly likely to mean that parents face a dilemma about whether to terminate a pregnancy (e.g. Bretelle et al., 2010; Signature Genomics, 2011). Numbers are rising fast, mostly in North America and Europe but also in India, Thailand and elsewhere, and 22q11.2DS is the focus of a growing array of medical clinics and activist organizations. But how did this come to pass?

The case of 22q11.2DS demonstrates that observations from genetics can be used to reconfigure medical classification in ways that have not been previously addressed in the social studies of science and medicine. In order to understand 22q11.2DS we cannot rely on the concept of 'geneticization' – Lippmann's term for the idea that categories of human difference would be "reduced to our deoxyribonucleic acid (DNA) codes" (1991, p. 19). Rather, we need to examine how research on the 22q11.2 microdeletion was actually productive of a new medical condition. It is more useful to think about 22q11.2DS as a case of 'genomic designation': a condition that is discovered, diagnosed and delineated on the basis of an observable characteristic of the genome that does *not* line up with any previously recognized category of person or indeed with any clinical diagnostic criteria (Navon, 2011). However, we will see that there is a crucial difference between 22q11.2DS and the initial case study of genomic designation, 22q13 Deletion Syndrome (now known as Phelan-McDermid Syndrome): while 22q13DS was never thought

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to have anything approaching a one-to-one relationship with an existing disorder, 22q11.2DS was not cut from whole cloth. Rather, the 22q11 deletion was initially posited as an etiology for DiGeorge Syndrome and then several other rare conditions. In its complex reconfiguration of biomedical subfields, nosology and medical populations, the 22q11.2 microdeletion suggests that we should pay close attention to the multiple pathways to the genomic designation of medical conditions.

We examine 22q11.2DS by attending to the development of three closely related, but analytically distinct kinds of biomedical phenomena: clinical disorders, genetic abnormalities, and genomically designated syndromes. The current case starts with a number of fairly rare *clinical* disorders, primarily DiGeorge Syndrome, VCFS and Opitz G/BBB Syndrome, with their own symptomatologies and independent origins as medical conditions. Then there is the genetic abnormality that came to be associated with those clinical conditions, the 22q11.2 microdeletion: the observation of cases, through genetic testing, of a deletion of DNA from site 11.2 on the long arm of the 22nd chromosome. Finally, a new category emerged that subsumes the above clinical conditions —what is now called 22q11.2 Deletion *Syndrome*. Analyzing the dynamics among these objects of knowledge in the case of 22q11.2DS, this paper presents a mechanism – the unification of fields – whereby genetic mutations can be mobilized to reconfigure medical classification.

To examine this process of unification we use novel citation analysis techniques supplemented by qualitative historical and IRB-approved fieldwork research to show how 22q11.2DS emerged as an object of knowledge. We begin with a review of the literature on 22q11.2DS and related conditions, followed by a review of the pertinent social scientific literature. Then, we describe our citation analysis strategy, extending the technique of Shwed and Bearman (2010) for mapping the structure and community salience of scientific literatures. We then present our results and argue that the genetic deletion at 22q11 was more than just an etiological finding: it was the 'boundary object' (Star & Griesemer, 1989) that unified otherwise disjunct fields of research and made possible the hybrid field in which 22q11.2DS could emerge as a qualitatively new medical condition. We therefore provide a targeted account of 22q11.2DS's conditions of possibility (Foucault, 1973, p. xix) by modeling its emergence from older fields of biomedical research. In so doing, we contribute to our understanding of the way that observations from genetics can reconfigure categories of medical classification and produce new ways of understanding human difference.

Literature(s) review

22q11.2 Deletion Syndrome has been the subject of over four hundred biomedical papers, while many more have investigated the medical implications of the microdeletion at 22q11.2. However 22q11.2DS has never been a subject of social scientific analysis despite its growing prevalence and, as we will argue, its capacity to speak to key issues in the social studies of genetics and medicine. This section will therefore review two disparate literatures – the extensive bioscientific literature on 22q11.2DS and the social scientific literature that has neglected it – in order to suggest that each has something to learn from the other.

The biomedical literature on 22q11.2DS

Reading the biomedical literature one is struck by the way 22q11.2DS is often treated as synonymous with other diagnoses, in particular DiGeorge syndrome and Velocardiofacial (VCFS)/Shprintzen syndrome. The literatures on DiGeorge Syndrome and VCFS may be traced back to papers in 1968 (DiGeorge) and 1978 (Shprintzen et al.) respectively, and other syndromes like Opitz G/BBB Syndrome, conotruncal anomaly face syndrome and Sedlakova syndrome similarly predate 22q11.2DS and are often considered to be subsumed by it. As a set of practical guidelines for 22q11.2DS recently published in *The Journal of Pediatrics* put it:

> Although clinically under-recognized, 22q11DS is the most common microdeletion syndrome (MIM#188400/#192430), with an estimated prevalence of 1 in 4000 live births. However, the actual occurrence may be higher because of variable expressivity…The 22q11.2 deletion is the second most common cause of developmental delay and major congenital heart disease after Down syndrome, accounting for approximately 2.4% of individuals with developmental disabilities and approximately 10% to 15% of patients with tetralogy of Fallot. 22q11.2 deletions have been identified in most patients with DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome and in a subset with autosomal dominant Opitz G/BBB syndrome and Cayler cardiofacial syndrome. Although this list of associated disorders may appear quite perplexing, it is understandable because the diagnoses were originally described by clinicians concentrating on their particular areas of interest. After the widespread use of FISH, however, patients with a deletion became collectively referred to by their chromosomal etiology: the 22q11.2DS (Bassett et al., 2011, p. 2).

Similarly, a review in *Newborn and Infant Nursing Reviews* (Miller, 2008, p. e11) tells us that 22q11.2DS "encompasses" what "were once thought to be different conditions with different diagnoses." One could cite many similar passages. Indeed since Wulfsberg et al.'s (1996) paper 'What's in a name?' the situation has often been likened to the parable of the blind men studying different parts of an elephant, sometimes even with a cartoon '22' elephant to illustrate the point (McDonald-McGinn, Zackai, & Low, 1997, p. 247).

But what are we to make of this nosological framework? Does 22q11.2DS 'encompass' these older syndromes because the deletion simply helped biomedical experts to see a clinical syndrome that they were previously blind to? The situation is far more complex. First, the proportion of people who are diagnosable with the clinically delineated syndromes listed above who also have a 22q11.2 microdeletion varies, but none approaches 100%. Thus in contrast to Down syndrome, this is not a straightforward case of a genetic etiology being discovered for an already-extant diagnostic category. Second, 22q11.2DS's clinical profile consists of more than 180 phenotypes, many of which are observable in only a small minority of cases and were not part of the profile of the clinical conditions with which the 22q11.2 deletion came to be associated. Finally, it is *not* necessary for a subject to be diagnosable with one of those longer-standing syndromes, or indeed with any clinically diagnosable condition, for them to be diagnosed with 22q11.2DS.

Consider this passage from a review in *Genetics in Medicine*, which follows a discussion of the multiple syndromes now associated with 22q11.2 deletions:

> Although the deletion is identical in most patients studied, the phenotype varies greatly. Goodship et al. report a case of monozygotic twins with 22q11DS where one twin's phenotype is more severe, showing that genotype alone does not account for the presence or absence of various features of 22q11DS. More than 180 clinical findings have been associated with 22q11DS… Both the number of organ systems involved and severity of involvement vary. Severe cases may result in neonatal death, whereas mildly affected individuals may

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