Abstract

Fleck and Kuhn suggested that scientific “facts” are constructed by a professional community instead of being discovered. This is examined using recessive inheritance for Friedreich Ataxia (FA). Sibling recurrences were known early on, but, for well over half a century, it was described as hereditary, which meant transmitted from generation to generation. Several factors were involved. First, FA is extremely variable, and overlaps with other disorders, making it seem like part of a spectrum, instead of a distinct unit trait suited to Mendelian analysis. Second, a medical system for inheritance based on a hereditary force for constancy with effects throughout life had overlapping doctrines central to analyses: Blastophoria (toxic damage to inheritance), Degeneration, Neuropathic Inheritance, and Polymorphism (several forms with one cause). Different factors could weaken the force, predisposing to a wide range of problems in the next generation, making it hereditary. Manifestations depended on interactions with other factors, and could vary widely, but the nervous system was especially vulnerable. These concepts were incompatible with the Mendelian inheritance of a specific, stable gene linked to a unique phenotype. Changes in medical experience let physicians deconstruct older “facts” about FA, making it a recessive at long last.

Keywords: Ataxia; Friedreich ataxia; Heredity; Recessive inheritance; Tabes dorsalis.

Introduction

Fleck [1] and Kuhn [2] suggested that scientific “facts” are constructed by a professional community instead of being discovered. Analysis of the idea of Tay-Sachs disease as a recessive supports this as basic medical issues as older concepts of inheritance affected how physicians were able to use genetics [3]. Here, another “fact”, Friedreich Ataxia (FA) as a recessive disorder, is used to further investigate these issues. This is of particular interest since it was first described as hereditary [4-8] which meant transmitted from generation to generation [9]. Clinical variability and overlap with other disorders interfered with delineation, but there was also an important role for older medical concepts of heredity that supported non-Mendelian approaches.
Background

Ataxias are, roughly speaking, problems with coordination. Many are genetic, often with additional neurological findings. In some families they run true, while others show incredible variability, and often overlap. Several genes can give similar findings, and in some cases dominant, recessive and sex-linked forms are clinically identical. Because of these issues, many were grouped together as spino-cerebellar ataxias, [10] after the two most frequently affected areas.

A full review of FA's clinical and genetic aspects can be found in Bürk [11]. To summarize, FA is the most common inherited ataxia. Onset typically starts with gait issues between the ages of 5 and 15, but varies from under 18 months to over 60 years. Problems slowly worsen and spread as muscles weaken and deteriorate, especially in the feet, lower legs, and hands. Tendon reflexes, and often sensation, are lost. Speech slowing and slurring, and easy fatiguability develop. Scoliosis is common. Heart disease often appears, and sometimes diabetes. Hearing or eyesight can be lost. The rate of progression varies, and life expectancy is reduced.

At least 95% of cases are due to homozygosity of a single recessive gene, either with a standard mutation, or with a triplet nucleotide repeat that affects function [12]. Interestingly, about 25% of patients have a genetic abnormality without meeting clinical criteria, giving FA without ataxia [11].

Although rare (roughly 2 to 4 cases per 100,000), [11] it fascinated neurologists, in part because of its variability, receiving far more attention than numbers alone would warrant. It was first delineated by Friedrich in 1863, with an inherited component postulated from the start. However, it wasn't until the mid 20th century that its recessive nature was fully established, and it was long considered hereditary, that is, transmitted from generation to generation.

Although issues involved unusual genetic findings and clinical variability, there were also problems related to traditional medical concepts of heredity as a transmitted changeable force that acted throughout life [3].

1. Aspects of particular importance influences, especially alcohol, later referred to as Blastophoria [13,14].
2. Degeneration, or Degenerate Heredity, a progressive weakening of the force, especially when higher functions were involved [14];
3. Neuropathic inheritance, a general susceptibility to nervous system problems, including mental abnormalities, and part of a belief in diatheses, predispositions with vulnerabilities to a variety of factors [15]; and
4. Polymorphism. A unitary something in the neuropathic or psychopathic inheritance that makes itself manifest under many forms [13].

Delineation: In the 19th century, the most frequent cause of ataxia was what we now know as spinal cord...
syphilis affecting the position sense, giving a typical clumsy gait. In 1858 Duchenne, the great French neurologist, differentiated this from other entities as locomotor ataxie [16]. This became a synonym for tabes dorsalis [17], a far older term that Romberg had appropriated in 1846 for the same condition [18]. It was originally thought to result from sexual excesses, or other influences that weakened the body. While a role for syphilis was suggested early on [19], it wasn’t until 1875 that a unique connection was emphasized, [20] and many physicians were unconvinced for decades after.

Virchow, the famed pathologist, objected to using a general symptom to describe a specific disease [21]. And here, Friedreich, a German neurologist, made an observation that seems to support nonspecificity. In five papers from 1863 to 18774-8 he noted 3 families with 9 cases of locomotor ataxia and other findings—what we now know as FA. Friedreich actually believed that both conditions were syphilitic, and that differences depended upon the extent of spinal cord involvement, with FA primarily affecting the medulla oblongata.

He saw this as a hereditary disorder, even though he invoked syphilis. But there was no contradiction: Traits weren’t necessarily inherited, but predispositions were, with possibilities for additional potentiating causes. So, similarly, for tabes dorsalis, Charcot saw heredity as the primary cause, and syphilis merely a precipitating factor [22].

However, hereditary meant across generations. Findings in siblings alone, as Friedreich described, were considered familial [9]. But, here, it was felt that ancestors had passed on predisposing factors—“hereditary’ is employed here in the widest sense. Not only direct heredity, from one generation to another is implied, but also those cases are included which occur in several members of the same generation; we have even noted that Friedreich’s disease may occur sporadically. It is more proper, therefore, to speak of ‘family ataxia,’ as has been proposed by various authors. But as we have seen in most cases, perhaps in all, there is a congenital [i.e., present at birth] agenesis or hypoplasia of the cord or cerebellum, the etiologic factors must be present in the ascendants; in this sense we speak of hereditary ataxia” [23].

Onsets after a period of normal development suggested an inborn weakness that other factors might bring out. Edinger felt that syphilis weakened the system, causing certain nerve tracts to hyperfunction, with over consumption of nerve-substance [23]. In 1883, Rutimeyer proposed “a primary systemic sclerosis developing on a hereditary foundation” [23]. So, “often the first symptoms of the disease have been observed after some acute infection... Starr is even of the opinion that in hereditary ataxia there is less of a congenital lack of development than an affection of the entire nervous system appearing in connection with an infectious disease... We may assume that the tracts which serve coördination are especially exposed to the toxic actions of the acute infections. In favor of this view is the fact, emphasized by Friedreich, that if in the course of hereditary ataxia an infectious disease (enteric fever) develops, the course and severity of the clinical picture are influenced in an exceedingly unfavorable manner” [23].

Friedreich noted alcoholic fathers in two families, and one widow stated that all her affected children had been conceived while the father was drunk. Alcoholism was a sign of neuropathic heredity (as well as a cause), and other components were seen in relatives of affected cases, although inconstant and varied, e.g..
Ladame [21] presented pedigrees with chorea, Bright’s disease of the kidney, insanity and convulsions, and Whyte, noting affected patients with a sib with a brain tumor, felt that “the family had a strong neuropathic tendency, and it is of course quite possible that two members of such a family might have Friedreich’s disease and a third a cerebellar tumour without Friedreich’s disease” [24].

Some felt that FA was a tabes dorsalis variant not worth separating out, or a form of multiple sclerosis, or even a combination of the two. But, by the 1880s it was seen as a disease in its own right, although limits were still poorly defined: In 1898, Whyte spoke of “transition forms” between FA and tabes, or cerebral diplegia (a form of cerebral palsy) [24]. Overall, there was a tendency to label any hereditary or familial ataxia as FA, plus a few neurological disorders where ataxia wasn’t even a real problem!

In 1893, Pierre Marie suggested a different type of ataxia in several such families, beginning later, with decreased reflexes, often abnormal eye movements, and tending to be overtly hereditary, i.e., obviously transmitted from parent to child. Despite these commonalities, the cases that Marie reported probably represented a variety of genetic disorders, with perhaps as many conditions as there were families! [25].

Marie suggested a single nervous system “heredodegeneracy,” his cases having more cerebellar involvement than FA, [26] but still part of the same spectrum. Sometimes, “symptoms varied in the course of the disease. Anatomically, transitional cases were also noted, and in some besides hypoplasia of the spinal cord the same condition was present in the cerebellum. Clinical and anatomical experience permits the view that the different varieties of hereditary ataxia are nosologically connected, that Friedreich’s disease and Marie’s herédo-ataxia cérébelleuse and the transitional forms, clinically and anatomically, present one form of disease which is characterized by the family appearance, progressive ataxia, and in which other symptoms may present the greatest variety, according to the distribution of the congenital hypoplasia and the intensity and extent of the columnar [spinal cord] sclerosis. The greatest number of authors incline towards this opinion” [23]. Or, in Russel’s words, “In fact, no line can be drawn between the two types either clinically or pathologically” [23].

This extended to other disorders: “many instances of transitional forms have been described from both the clinical and the pathologic viewpoint, particularly among the syndromes of Friedreich’s ataxia, Marie’s heredocerebellar ataxia, Charcot-Marie-Tooth peroneal muscular atrophy, hereditary spastic paralysis and Leber’s hereditary optic nerve atrophy” [27]. These heredodegenerative diseases included the disorders later known as the spinocerebellar ataxias although, conceptually, heredodegenerative diseases all had the same cause, while spinocerebellar ataxias had different ones.

There were some skeptics- Freud felt that “no trace of any accessory aetiological factor is ever found” for FA [28]. However, Russel’s view [23] was more typical, with FA “a congenital inherited and inherent lack of vitality in certain parts of the nervous system. Other stigmata of degeneration are not lacking, and cases have been reported associated with conditions of infantilism, feminism, maldevelopment of the testicles, and so on. The congenital tendency is shown by the usual occurrence of the disease in several members of the same family, its onset at approximately the same age, and the similarity of the type of developed disease in the different members affected. A neuropathic diathesis is present in most cases, as is frequently
shown by the occurrence of hysteria, migraine, epilepsy, or insanity in collaterals or ancestors (He also
discusses alcoholism as a cause). Hereditary lues [syphilis] and tuberculosis may be predisposing causes.
Consanguinity in the parents has been reported in many of the cases, and doubtless had some influence on
the causation of the disease. Any fall, injury, or infectious disease may appear to determine the onset, and
any cause acting as a depressant to the vital forces may produce a rapid advancement of the symptoms.”

We see this basically unchanged in a 1938 neurology text by Bing, [29] a highly respected Swiss
neurologist whose books went into many editions and translations. His views were mainstream, and still
cited on this in 1954 [30]. I would like to use an extensive quote here to show ideas and terms clearly
incompatible with genetics that would not have been out of place 50 years earlier.

So, FA “usually affects several members of the same generation. It is not only a disease of a single
individual but of an entire line of descendants as well. From generation to generation the disease appears at
an earlier and earlier age. It sometimes happens that the disease skips several generations, only to appear in
a later generation (atavistic reversion). That the heredity is sometimes latent has been convincingly shown
by tracing several patients to a common ancestor who lived during the sixteenth century. The descendants
of this man were distributed throughout six collateral lines, the disease appearing only in the eleventh or
twelfth generation. The incidence of consanguineous marriages with dying out of certain branches and a
history of heavy drinking were comparatively frequent among those of the intervening generations.”

“Evidence that Friedreich’s disease is an expression of an hereditary defect is strengthened by the fact
that the most varied congenital defects and malformations are to be found in individuals with this disease.
[He listed hypospadias, facial asymmetry, a “mongoloid” face, and spinal cord and skeletal anomalies].
Friedreich’s disease sometimes occurs in combination with other heredodegenerative diseases; for
example, I have seen hereditary ataxia and muscular dystrophy in the same person. Killarits had observed
a combination of Friedreich’s disease and Huntington’s chorea in a patient. One of my patients, a young girl,
had a father with bilateral club foot”.

“Jandrássik writes ‘In many families very striking peculiarities occur. Some lose their hair prematurely;
in others the [spinal cord] pyramidal tracts degenerate.’ When an heredofamilial disease appears in the
family for the first time, the cause can frequently be laid to certain blastophthoric i.e. germ-injurious,
influences in the parents, for example, alcoholism. In many cases the information is volunteered that the
affected children were begotten while the father was in a state of drunkenness. Parental consanguinity
and disproportionate ages of the parents have also been considered blastophthoric factors. According to
Ohmstede, there is pronounced injury of the germ plasm in mothers whose reproductive powers become
exhausted by too much childbearing” [29].

Problems with defining the disorder were ongoing. For example, Roussy-Levy hereditary flexic
dystasia, a disorder of coordination, has some very real differences from the true ataxias. Roussy and
Levy “stressed the absence of cerebellar signs, speech disturbances, Babinski sign, and nystagmus,” [31]
all characteristics of FA, yet Rombold and Riley also described it at the same time as “an abortive form of
Friedreich’s disease” [32]. These issues continued past the middle of the century, e.g. in 1958, Sylvester
reported a dominant condition with optic nerve atrophy and nerve deafness as “unusual findings in a family with Friedreich’s ataxia” [33].

Given the confusion over what FA actually was, questions over inheritance are hardly surprising. Garrod called it a dominant in 1927, [15] and Bell and Carmichael’s encyclopedic review of inherited ataxias concluded that it could be dominant, recessive, or sex linked [34]. Cobb saw FA as “largely dominant” [35]. Grinker and Bucy felt that “direct heredity is rare but several siblings may be afflicted in the same manner” [36]. For Ford, it was “definitely hereditary as well as familial and may, in many instances, be traced back for a number of generations. It occurs in both males and females, although somewhat more frequently in the former than the latter. The mode of transmission is obscure, and can scarcely be reconciled with any simple Mendelian law. Some authors postulate two morbid factors, one of which is dominant and one recessive.” [37] Schut’s 1954 classification of ataxias lists all three standard Mendelian modes, and breaks FA in each mode into a pure form and fourteen types of admixtures! [30].

Certainly FA was not the only Mendelian neurological disorder with incorrect attributions, e.g. Tay Sachs disease and Werdnig-Hoffmann disease, both recessives, were once seen as dominants [3].

For a variety of reasons, older ideas of inheritance were out of style by the second half of the 20th century. Neurologists, who often saw non-specific disorders with uncertain patterns of inheritance, held on longer than other physicians, but they, too, finally accepted genetics, along with shifts to narrower definitions of disorders [3]. Clinical diagnostic criteria for FA were established in 1976 and refined in 1981. With this, its recessive character became obvious, and a specific gene was mapped in the mid 1990, and isolated soon after. Interestingly, it was then found that up to 25% of genetic cases had findings differing from standard clinical criteria [11].

**Discussion**

FA, and its appearance in siblings, was well known by the late 19th century, but a definitive link with recessive inheritance didn’t occur until the second half of the twentieth. This supports Fleck and Kuhn’s concept of the construction of facts by a professional community, [1,2] a process that had several facets here.

One involved clinical definition. FA is highly variable, and overlaps with other disorders, often also variable and hard to define. This made FA part of a spectrum, instead of a distinct biological entity, reflecting how physicians saw diseases in general [3].

Another was a medical model of inheritance. Here, several overlapping doctrines explained the inheritance of FA in a medical context incompatible with Mendelian ideas of a specific, stable gene uniquely linked to a defined phenotype.

This included links to blastophoria, with damaged inheritance and/or germ cells, issues generally associated with neurological disorders, but particularly strong with FA, as well as a degeneration with a worsening over generations. A wide range of manifestations in families strengthened the case for a variable
heredity. In contrast, for another recessive neurological disorder, Tay-Sachs disease, a more consistent classic phenotype, although not always appreciated, meant less of an emphasis on such factors [3].

A belief in diatheses [15] emphasized variable tendencies, especially with a nonspecific neuropathic inheritance [13]. 271 that overlapped with a more general degenerate heredity [14].

As causal definitions of disease replaced older clinical approaches, [38] overlapping etiologies became less likely, and links to specific genes increasingly logical. Neurologists, who often saw nonspecific problems without any clear genetic pattern (e.g. schizophrenia), were among the last to accept the new order. And here, FA, which lacked a specific test until recently, took especially long to become a clear recessive.

Integrating Mendelism into medicine involved more than just applying a new paradigm to old information. Other doctrines developed for, and supported by, general medical experience going well beyond FA had to be replaced, and “facts” that arose from, and supported older ideas, had to be deconstructed.

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