

Francis Galton: his approach to polygenic disease

ABSTRACT – Gregor Mendel is considered to be the founding father of modern genetics, and his laws of inheritance have led to the successful analysis of rare monogenic diseases such as cystic fibrosis, Duchenne muscular dystrophy, familial hypercholesterolaemia, and many others. Francis Galton chose multifactorial inheritance as his starting point, and his methods of analysis have withstood the test of time. He used detailed family records to study the inherited tendency of complex traits between parents and offspring, and between identical and non-identical twins to refine the analysis, and devised new statistics to attempt to measure the extent of inheritance. For all these reasons, he can be considered the founding father of quantitative genetics.

Gregor Mendel and Francis Galton were both born in 1822. Mendel is considered to be the founding father of modern genetics, and the last two decades have seen the brilliant analysis of rare monogenic disorders that follow the principles of Mendelian inheritance. The genes for cystic fibrosis, Duchenne muscular dystrophy, familial hypercholesterolaemia and many other disorders have been identified and isolated. Methods for somatic gene replacement have been developed and implemented for adenosine deaminase deficiency and familial hypercholesterolaemia. These have been based on a rigorous study of large pedigrees for clinical features of the disease, biochemical defects or DNA markers, and then the application of Mendelian laws of inheritance for the analysis.

More recently, attention has turned to the analysis of some of the common multifactorial disorders¹, such as diabetes mellitus, premature coronary heart disease, some types of cancer, and psychiatric disease such as schizophrenia and bipolar affective psychosis. Although such disorders are clearly transmitted in families, there appears to be no simple pattern of Mendelian inheritance for use in the genetic analysis. There is variable penetrance of the disease in families, and it is not possible to distinguish clinically between presumed heterozygous and homozygous states. The clinical features, if anything, appear to 'blend'; the laws of segregation do not hold, in that each subject does not appear to possess only two genes to account for the transmission of the disease; and the distribution of the disease phenotype in pedigrees does not suggest independent assortment – that is, does not

follow Mendelian proportions for either recessive or dominant traits.

Francis Galton chose this field of multifactorial inheritance as his starting point, and attempted to explain the inherited tendency between parents and offspring for stature, skin or eye colour, and liability to develop asthma and pulmonary tuberculosis². It may be instructive to examine his approach to the problem of complex inheritance, and to see how far the subject has progressed in the 100 years since the publication of his book *Natural inheritance* in 1889³.

Francis Galton (1822–1911) studied medicine (but never qualified) at Birmingham (1838). He left the Birmingham General Hospital for a variety of health reasons, for example, severe headaches and a 'very uncomfortable mind, but I shall soon get over all the hospital horrors etc, etc'⁴. In 1839–40 he studied at King's College, London, taking – and enjoying – courses in forensic medicine, chemistry, surgical operations and botany, but by May 1840 he wrote to his mother that he intended to go to Liebig's laboratory in Giessen:

Liebig is the first Chemist (in organic chemistry) in the world. In his Laboratory there is every opportunity for getting on, in addition to the certainty of a knowledge of German⁵.

In October 1840 he entered Trinity College, Cambridge, to study mathematics, but again he had a bout of ill-health:

... the reason why I write in pencil is as I am lying on my back I can't get a pen to write; I have been confined to my bed for some days, rheumatism, not over-working, but will shortly be released⁶.

The illness had in fact been more serious than revealed in his letter, with further bouts of recurrent ill-health. In the May examinations at Trinity in 1841 he obtained only a Third Class degree. By 1843, he had a complete breakdown in his health, and was unable to concentrate on mathematics because of severe dizziness and palpitations. He finally decided to give up reading for his mathematics honours degree.

Galton's early research included work on the inheritance of character traits such as intelligence, ability and sensory perception, but he also proposed and developed methods for the study of the inheritance of complex disorders such as 'consumptivity', cancer and asthma. In this field, he considered himself to be:

a surveyor of a new country and to endeavour to fix, in the first instance, as truly as I could the position of several cardinal points⁷.

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In his view, these cardinal points were:

- defining the phenotype
- using identical and non-identical twins
- devising statistical tests for the proof of inheritance.

Defining the phenotype

In the absence of any good biochemical or bacteriological markers for disease, Galton had to rely on good clinical records. A sample of his schedules for hereditary disease (with the individual names changed) is shown in Table 1. He collected 160 usable family records with an average of 75 individuals per record, and thus recorded approximately 12,000 disease states and 2,000 causes of death – expending £500 of his own money in collecting this material⁷. He demonstrated that his collected data were free of sampling bias by showing that deaths due to cancer, consumption or suicide did not appear either more or less frequently

in his records than in the ordinary Life Assurance Society mortality tables.

To illustrate his method, he studied 14 of the pedigrees in which 50% of the deaths were due to lung trouble, which he graded from high to low suspicion for the diagnosis of tuberculosis. He found that nine of the 14 mothers were consumptive, which led him to a tentative conclusion that consumption, whilst partly due to the inheritance of a tuberculous diathesis, could also be transmitted by infection⁷. He admitted that the data were very 'slender', but considered that the general approach of knowing the frequencies both of a particular disease (preferably non-infective) in the community and of cases in the offspring of affected parents may give a value for the correlation between parents and offspring, and therefore some indication of the intensity of heredity in that particular disease.

He had finally to admit that he obtained practically nothing of value from this study. Thus, he writes:

Table 1. Sample of one of Galton's schedules for heredity of disease.

Father's name: James Gladding, Mother's maiden name: Mary Claremont				
Initials	Kin	Principal illnesses and ailments	Cause of death	Age at death
JG	Father	Bad rheum. fever; agonising diarrhoea; bronchitis, pleurisy	Heart disease	54
RG	Brother	Rheum; gout	Apoplexy	56
WG	Brother	Good health except gout; paralysis later	Apoplexy	83
FL	Sister	Rheum. fever; rheum.gout	Apoplexy	73
CG	Sister	Delicate (inoculated and died)	Smallpox	?
MG	Mother	Tendency to lung disease; biliousness; frequent heart attacks	Heart disease and dropsy	63
AC	Brother	Good health	Accident	46
WC	Brother	Led a wild life	Premature old age	62
EC	Brother	Always delicate	Consumption	19
FR	Sister	Smallpox three times	General failure	85
RN	Sister	Bilious; weak health	Cancer	50
LC	Sister	?	Fever	21
Offspring				
MG	Brother	Inflam.lungs; rheum.fever	Heart disease	17
KG	Brother	Debility; heart disease; colds	Consumption	40
GL	Sister	Bad headaches; coughs; weak spine; hysteria; apoplexy	Paralysis	50
FS	Sister	Bad colds; inflam.lungs; hysteria	Living
RF	Sister	Infantile paralysis; colds; nervous depression	Living
LG	Sister	Inflam. brain, also lungs; neuralgia; nervous fever	Living
Space left for remarks:				

Suggested additions, columns made for occupation and environment.

I had hoped even to the last moments, that my collection of Family Records would have contributed in some small degree towards answering this question, but after many attempts I find them too fragmentary for the purpose. It was a necessary condition of success to have the complete life histories of many Fraternities who were born some seventy or more years ago, that is during the earlier part of this century, as well as those of their parents and all their uncles and aunts. My records contain excellent material of a later date, that will be valuable in future years, but they must bide their time; they are insufficient for the period in question. By attempting to work with incomplete life-histories the risk of serious error is incurred⁸.

Twins (identical and non-identical)

He was more fortunate with his study of twins. There was a previous large scientific literature relating to the anatomical and physiological aspects of twins (Galton quotes frequently from *Die Lehre von den Zwillingen* by L von Kleinwachter, Prague 1871), but before Galton's studies there appeared to be no literature attempting to measure the extent of inheritance of psychological traits in twins. He sent circulars of enquiry, similar to his family records, either to twins themselves or to near relatives, receiving 120 responses from which he selected 80 pairs of identical twins and 20 pairs of non-identical twins⁹. Tests for di- or monozygosity were of course not available, but it was known that twins could develop either from separate ova or from two germinal spots in the same ovum.

His chosen question was whether heredity or environment was the major determinant for the occurrence of either contagious or non-contagious disease. From the 80 pairs of identical twins, he obtained 35 case histories suitable for the study of disease. Seven twin pairs were concordant for some special disorder, including structural defects of the hands, rheumatic ophthalmia, asthma, monomania

(including paranoid delusions, hallucinations and depression), and other forms of insanity. He also noted many other similarities, such as association of ideas, tastes and dispositions, which remained even after twin pairs had lived apart for many years in adulthood.

Conversely, with the 20 pairs of non-identical twins for which he had sufficient family and clinical records, he was struck by the dissimilarity of the case histories, despite at least 13 of these twin pairs having almost identical family and educational environments. Although much of this information was anecdotal, he found that with regard to the occurrence of disease and other physical characteristics (eg height, hair colour and eye colour):

there was no escape from the conclusion that nature prevails enormously over nurture⁹.

Statistical tests

Galton stated that the proof of such complex inheritance must, however, finally rest with statistics rather than with this anecdotal evidence. To what extent does factor A in a parent contribute to factor B in the offspring? His reply was that 'we must endeavour to find a quantitative measure for this degree of partial causation'.

Surprisingly, in 1875, he started to study the weights and diameters of sweet pea seeds in parents and offspring, and used the data to construct his first 'regression line'¹⁰. This is presented in Fig 1, and is perhaps the first regression line ever to be drawn. The correlation coefficient is 0.33. He also noted that as the size of the parent pea seed increases, so does the size of the offspring seed, but the latter does not reach the same deviation from the mean as the parent (ie the offspring is less a giant or a dwarf than the parent pea). This is Galton's phenomenon of regression to the mean. He reached the idea that the slope of the

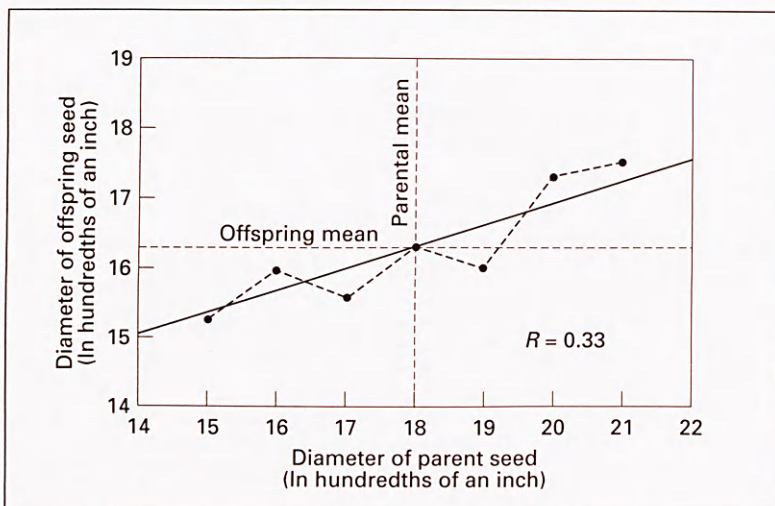


Fig 1. Galton's data on inheritance in size of parent and offspring sweet pea seeds (from his lecture to the Royal Institution, 1877¹⁰, redrawn by Karl Pearson in reference 8 and reproduced here by permission of Cambridge University Press).

regression line would measure the intensity of the resemblance between parent and offspring. If there were no slope, the diameter of the offspring pea would be the same for all diameters of the parent pea; if the slope was 45 (ie a slope of unity), the diameter of the offspring pea would be exactly the same as that of the parent, supposing that their means were the same.

He used this idea of regression to study the inheritance of human stature in 928 offspring correlated with mid-parental statures, and found the regression slope to be 33.3¹¹. He also attempted to use similar statistics to assess the inheritance of eye colour in 4,490 individuals from 168 three-generation families. The use of regression analysis to define a functional relation between two variable quantities has been in use ever since, and has been greatly refined into powerful statistical tests by Pearson, Spearman, Kendall, Cramer and others.

It is a remarkable coincidence that both Galton and Mendel should have used sweet or edible peas for their studies of heredity. Galton said he chose sweet peas because he would not be troubled to the same extent by variation in size of peas within the same pod as with the edible variety. It is not known whether he had heard of Mendel's work on edible peas, which was published in 1865 but went largely unnoticed in the European literature until 1900. It remains to be seen whether Galton's correlational calculus or Mendel's factorial analysis of legume heredity is of greater importance for the future studies of genetics.

Conclusions

The approach to the study of multifactorial inheritance has progressed in the last 100 years because of better definition of disease phenotype through the use of biochemical and cellular markers, and by the ability to perform structural and functional analyses of DNA. The basic approach, however, is due to Galton's pioneering contribution:

- collecting affected sib pairs, preferably mono- and dizygotic twin pairs;
- performing parent-offspring analyses and evaluating the degree of concordance for the disease pathology; and
- using refined statistical tests to quantify the degree of inheritance.

He is certainly the founding father of quantitative genetics. It is unfortunate that a large part of his work fell into disrepute in the 20th century because of his preoccupation with, and enthusiasm for, eugenics. His aims were to encourage 'superior' races or social classes to marry selectively and thus outnumber, and gradually replace, the 'inferior' races or classes¹². He wrote that there was no question of active suppression of the inferior races or classes as their decline would tend to happen naturally. These ideas were taken up and perverted by the Third Reich, with the well-known consequences. But his claim for fixing the position of several cardinal points in the field of quantitative genetics is amply justified by his discoveries.

Acknowledgements

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