



Old Mystery Solved: Achromatopsia, the Fuur Genealogy in Retrospective

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Abstract

In 1940 two Danish ophthalmologists published the largest known family with congenital total achromatopsia. The family inhabited a small island Fuur situated in a Danish fiord. In connection with the first International Congress of Human Genetics in 1956 an excursion was arranged to the island by Albert Francheschetti, for a closer characterization of the intrafamilial phenotypic variation. They also examined two brothers from an unrelated family with discordant phenotypes, complete and incomplete achromatopsia, respectively. The finding contrasted the prevailing “one gene-one disease” concept. Genealogical evidence indicates that the mutation was brought to the island by a male born about 1620. A molecular analysis of the large family revealed the most common *CNGB3* mutation in Europe (biallelic c.1148delC) to be causative. In the small mainland family a different homozygous *CNGB3* mutation was ascertained. A re-examination 25 years after the Fuur expedition showed unchanged phenotypes. This example illustrates problems arising due to our historically defined diagnostic taxonomy to characterize phenotypes. On the other hand, genetic classifications alone are also insufficient to meet the rising demands for genetic counseling and therapeutic inventions. A close integration of clinical and molecular genetic data has become mandatory in both research and daily practice.

Introduction

In 1900, following the re-discovery of Gregor Mendels “Versuche über Pflanzenhybride” (Experiments on plant hybrids) from 1866, heredity entered a flourishing pioneer period during the first half of the 20th century. In Denmark, Wilhelm Johannsen (1857-1927), professor of plant physiology at the University of Copenhagen worked with pure lines of the common bean. Based on his experimental results he coined the terms “genotype” and “phenotype”. After his death a grant was dedicated to educate a younger physician to qualify for a chair in human genetics, and with financial support from The Rockefeller Foundation, the Institute for Human Genetics and Eugenics was established at the Copenhagen University in 1938 and inaugurated with Tage Kemp, MD as its first director (Figure 1).

An intensive research developed during Tage Kemp’s leadership and a considerable number of medical genetic disease

monographies were published during the following years.

In August 1956 Copenhagen hosted the first International Congress of Human Genetics. According to a contemporary quote “The obvious country for the first meeting was Denmark, which, under the inspiring leadership of Professor Tage Kemp, is the genetically most thoroughly investigated country in Europe” [1]. The congress included 17 sections according to medical specialty. The ophthalmology section had 27 registered attendants among others Dr. G. Melvin Alper (1921-2013), Washington, prof. Max Bückler (1895-1969), Bonn, prof. A. Francheschetti (1896-1968), Geneva, prof. Wolfgang Jaeger (1917-1995), Heidelberg, prof. Arnold Sorsby (1900-1980), London, prof. E. Bernardo Streiff (1908-1988), Lausanne, and Dr. P. J. Waardenburg (1886-1979), Arnhem. A section “Hereditary Abnormalities of the Eye” consisted of 15 contributions among which three dealt with color blindness [2].



Figure 1: Professor Tage Kemp (1896-1964), Director of the University Institute of Human Genetics and Eugenics in Copenhagen 1938-1963. Photo kindly borrowed from Medical Museum, University of Copenhagen.

Congenital achromatopsia

Total color blindness, congenital achromatopsia with amblyopia, or rod monochromacy is a rare congenital hereditary condition with autosomal recessive inheritance, which - besides a complete inability to perceive colors - is accompanied by severely reduced visual acuity, photophobia and nystagmus. Later it was recognized that in addition to complete achromatopsia also incomplete forms exist. The two forms were differentiated based on color vision tests including spectral sensitivity recordings. With the development of electroretinographical (ERG) techniques it became evident that further clinical heterogeneity existed, and the term cone dysfunction syndromes was introduced to characterize mainly stationary conditions in contrast to the progressive cone dystrophies and cone-rod dystrophies [3]. The growing insight into the molecular background of the conditions led to new classifications, however, it was soon realized that also molecular genetic classifications covered a wide range of clinical heterogeneity.

The prevalence of achromatopsias with amblyopia is estimated to 1/30,000-1/50,000 worldwide. However, in genetic

isolated populations the frequency might be considerably higher. Such a case was reported by two Danish ophthalmologists, who in 1940 published an unusually frequent occurrence of individuals with total color blindness from the small island Fuur in the northern part of Jutland, Denmark with a population of about 1,600 individuals [4]. Based on family history they were able to reconstruct the pedigrees of two families, the larger of which counted 19 affected members among whom 13 were still alive. Furthermore, two living affected individuals belonged to a small and apparently unrelated family counting four affected individuals. Until then a limited number of small families had been published and the Fuur family was the then largest known family with congenital total achromatopsia and attracted attention among ophthalmic geneticists of the time.

The Fuur expedition 1956

In connection with the Human Genetics Congress, an expedition to the island Fuur was arranged under the leadership of professor Adolphe Franceschetti, and participation of professor Wolfgang Jaeger, David Klein from the Genetic Institute in Geneva, and Vagn Ohrt, head of the Department of Ophthalmology, Aalborg, Denmark. One of the aims of the expedition was to determine whether complete and incomplete cases of achromatopsia could be present in the same sibship. This had until then not been demonstrated and according the prevailing opinion among ophthalmic geneticists at the time, incomplete achromatopsia with amblyopia was due to a gene or genotype that differed from that of the complete type. In addition to color vision examination with Ishihara tables and the Nagel anomaloscope, the equipment of the expedition included instruments for spectroscopical and photometrical analyses. The results were published in 1958 [5]. It was shown that the two families on the island in fact were interrelated, and re-examination of 13 living individuals reported by Holm and Lodberg as well as an additional individual born 1940 disclosed uniform color vision tests and spectral sensitivity curves, thus confirming a constant intrafamilial phenotype, yet with individual variations in visual acuity and degree of photophobia. The Fuur achromats became widely known and were reported in detail in ophthalmic genetic textbooks of the time [6-9].

However, to the great surprise of the expedition team the examinations in two brothers from an unrelated small family where the parents were first-degree cousins revealed striking intrafamilial difference in the phenotype (Figure 2). This family living in a village on the mainland only a few kilometers from Fuur evidenced for the first time a case of complete and incomplete achromatopsia in the same family [5].

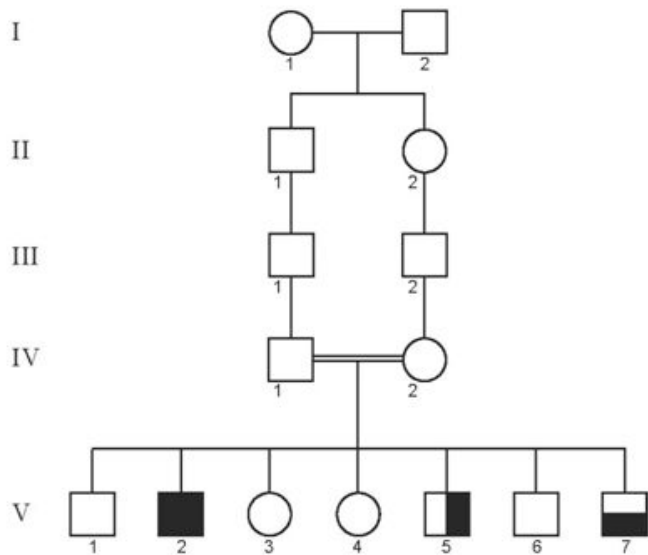


Figure 2: Pedigree of the small mainland family with both complete and incomplete achromatopsia. The parents to the siblings in Vth generation are second degree cousins. Symbols: quadrant = male, circle = female, filled= complete achromatopsia, vertically half-filled = incomplete achromatopsia, Horizontal half-filled = cone dystrophy with amblyopia and deuteranopia.

In 1981, 25 years after the Fuur expedition, a new examination of the two brothers (V:2 and V:5 in Figure 2) was performed in Heidelberg with all available methods [10]. The examinations fully confirmed the findings of the expedition. In the elder brother (V:2) a pure rod sensitivity curve was found, while in the younger (V:5) a residual cone function was present. It was concluded that the only explanation for the phenotypic difference was “the influence of a modifier gene which is located on another chromosome and is acting independently of the achromatopsia gene” [10].

Results

The Fuur Genealogy

Meticulous genealogical studies through many years have led to the establishment of “The Fur Base” with all known Fuur inhabitants from the period 1600 to 1930. The database consists of more than 10,000 individuals from more than 3,000 families. An algorithm developed to identify common ancestors of all the identified individuals with achromatopsia led to a single couple, Søren Nielsen Vandborg and his wife. His name is interesting; most often he was called Søren Nielsen, the surname being a patronym meaning “son of Niels”. In some other sources he is called Søren Vandborg, where Vandborg is the name of a village outside the island Fuur from where he may origin. He was born about 1620 and probably came to Fuur as a farmhand. Here he married Maren

Iversdatter, who most likely was a local girl. Søren and Maren had at least five children of whom three had cases of achromatopsia among their descendants.

In order to prevent inbreeding, it was in the 17th century in Denmark by law forbidden to marry even second cousins. Nevertheless, intermarriages among 94 of the 289 great-great-great-grandchildren (fourth cousins) of Søren and Maren was the reason why achromatopsia accumulated on Fuur creating a relative genetic isolate. In 1798 one of those pairs gave birth to a son (out of seven siblings), who became the first known person with achromatopsia on Fuur, more than 150 years after Søren Vandborg came to the island. When he registered for military service, he was diagnosed with “glaucoma on both eyes”. Twenty years later a pair of fifth degree cousins had seven children among whom three had achromatopsia. When one of them registered for service in the navy, he was diagnosed as “dayblind – almost completely blind”. He was categorized as seaworthy, because he participated in fishing in the fiord in spite of his handicap. In both cases, nothing is documented about their color blindness.

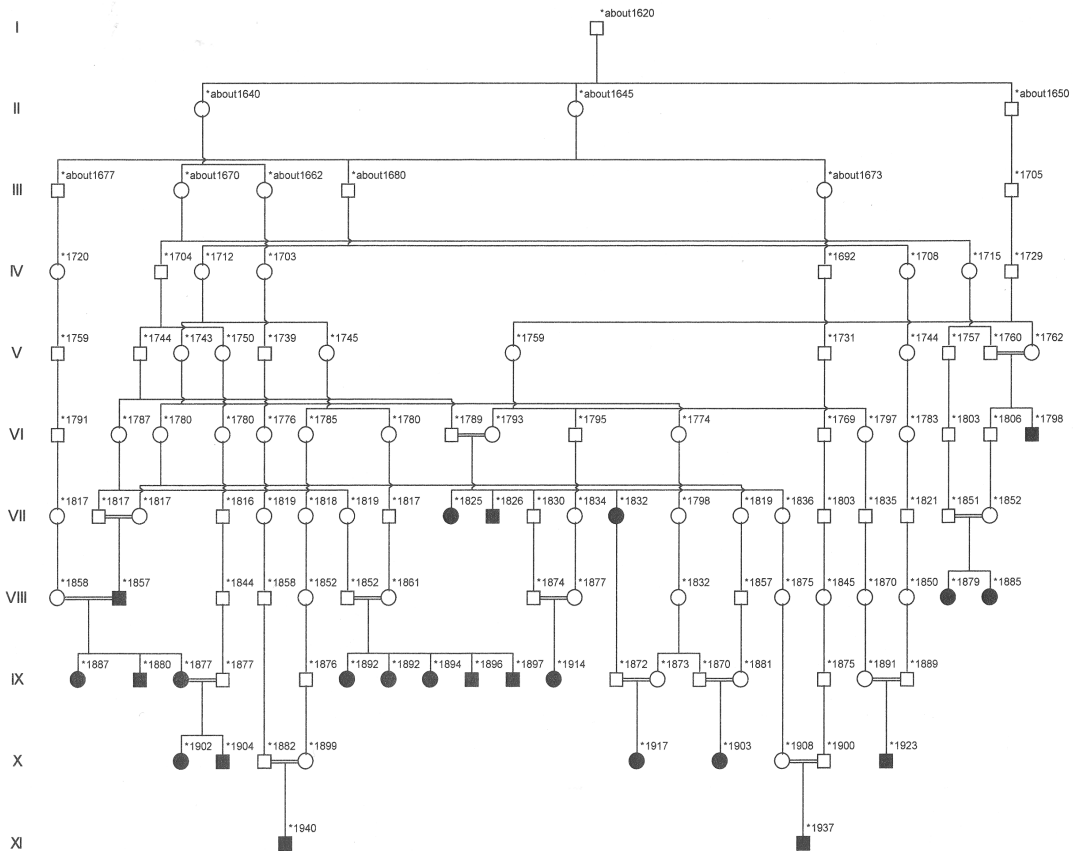
In the population census of 1845, where the place of birth was registered for the first time, 7.1% of the 966 inhabitants of Fuur, came from outside the island. In two neighbouring parishes on the mainland the corresponding percentages were 26.8% and 35%, respectively. In the twenties century the isolation came to an end, and the last individual with achromatopsia was born on Fuur in 1940, almost 300 years after the arrival of Søren Vandborg. Today more than half of the inhabitants of Fuur are born outside the island (Figure 3).

Examinations

We had the opportunity to re-examine the two brothers at the former National Eye Clinic for the Visually Impaired (NEC) in Denmark in 1992. The phenotype of the elder brother (Figure 2, V:2) with complete achromatopsia was unchanged and full field electroretinogram (ffERG) showed a normal dark-adapted rod response and no photopic responses to white, red, green and blue flashes. His visual acuity (VA) was unchanged: 0.1 monocularly and binocularly. He died in 1994.

The younger brother born 1947 with incomplete achromatopsia (Figure 2, V:5) had progressed into a complete form as measured with Nagel’s anomaloscope and he failed all four plates with Berson’s blue cone monochromacy test. The ffERG showed normal scotopic reaction and complete absent photopic responses. At the latest examination in 2001 ophthalmoscopy showed mottling of the macular pigment epithelium. The youngest brother (Figure 2, V:7) in this sibship of seven was born in 1954. When the Fuur expedition took place he was only two years old and he was not examined at that time. The first examination at NEC took place when he was 38 years old. According to history he had low vision from early childhood, but no nystagmus and

he was able to see colors. His VA was 0.2 in both eyes and 0.4 binocularly. Ophthalmoscopy showed slight paleness of the optic nerve heads, normally calibrated vessels, missing foveola reflexes, and a few hard drusen centrally. With Nagel’s anomaloscope he showed deuteranopia. He accomplished Berson’s blue cone monochromacy test and Farnsworth 100 hue was pathologic with 485 in error score and an axis of 485 mμ. The ffERG showed normal scotopic and photopic responses, with normal oscillatory potentials and normal photopic responses to red, green, and blue flashes. Goldmann perimetry with a small spot size showed no defects of the visual fields. In 2002 photopic multifocal ERG showed a central depression of 30% and pericentrally the responses were 25% of normal. At the last examination in 2005 the VA had dropped to 0.12 in both eyes.



The family of the Achromates on the island of Fuur in Limfjorden, Denmark

Figure 3: The reconstructed Fuur genealogy. All known individuals with an either established or probable diagnosis of achromatopsia are indicated by filled symbols. Affected individuals are connected in direct ascending line to the common ancestor born about 1620 through the most likely unaffected carrier ancestors (open symbols). Circles, females; quadrants, males. An asterisk marks the birth year of each individual.

Molecular Genetics

In 1998 a project aimed at the molecular genetic characterization of Danish citizens with a diagnosis of achromatopsia was launched at the former National Eye Clinic of the Visually Impaired. Among 82 affected living individuals 44 consented to participate in a molecular genetic project aimed at the identification of the genetic cause of the disorder. Three individuals in this cohort were born on Fuur in 1923, 1937, and 1940, respectively, and belonged to the large family investigated by Francheschetti in 1956. DNA was also obtained from the three affected brothers of the mainland family (Figure 2) and an

unaffected brother and sister. In both families homozygous *CNGB3* mutations were identified. The three probands from the large Fuur family carried the variant c.1148delC in homozygous state and clinical re-examinations confirmed a diagnosis of congenital complete achromatopsia. In the small family from the nearby mainland, surprisingly another homozygous variant c.1430_1431delinsC/p. K477Tfs*17 in *CNGB3* was present in the two elder brothers (V:2 and V:5) in which clinical examinations over a period of 45 years revealed a slowly progressive cone dystrophy phenotype. Notably the youngest brother (V:7) with low vision and deuteranopia carried the wildtype sequence on both alleles. Further efforts to find a mutation in the youngest brother included the red-green opsin (*OPN1LW/OPN1MW*) gene cluster, which was structurally intact, and sequencing of all coding exons did not identify any point mutation. Finally performing a Mendeliome NGS sequencing covering all protein-coding regions of known disease-causing genes (2016) did not uncover any disease-causing variant explaining his condition.

Discussion

The diagnostic vocabulary for many eye diseases was created more than a Century ago based on symptoms and obvious signs, not least those observed with the ophthalmoscope, which was invented by Hermann von Helmholtz (1821-1894) in 1851. With the invention of new instruments and examination methods, new subclassifications developed as in achromatopsia, where studies in color vision introduced the term incomplete achromatopsia, which among others included X-linked blue cone monochromacy and oligo-cone trichromacy. Among clinicians, “lumpers” and “splitters” tried to find new concepts to characterize an observed phenotype [11]. Achromatopsia was lumped into a category named cone dysfunction syndromes [3] in contrast to the progressive types of photoreceptor disorders, cone and cone-rod dystrophies. Additional complexity has been added with the knowledge of genetic variants in families and individuals adding a new aspect to the overall taxonomy of genetic disorders and the rising demands of genetic counseling and the development of therapeutic concepts [12]. Molecular genetic investigations over the last 20 years has so far led to the identification of six genes causative for autosomal recessive achromatopsia, *CNGB3*, *CNGA3*, *GNAT2*, *PDE6C*, *ATF6*, and *PDE6H* [13]. Mutations in *CNGB3* are the most prevalent cause of achromatopsia among Caucasians of European descent mainly due to an exceptionally high frequency of the c.1148delC mutation in this population accounting for >70% of all *CNGB3* mutant alleles [14,15].

The “mystery” arose due to the false “one gene - one disease”

concept of the time. Different pathogenic variants in most of the known achromatopsia genes may lead to various phenotypes from complete to incomplete achromatopsia, oligo-cone trichromacy and cone dystrophy, depending on the joint effect of the two alleles. However, the discordance in the phenotypic presentation of two elder brothers, which puzzled the 1956 expedition members and the authors of the follow-up study in 1981, is not reflected in the principle molecular genetic findings since both were homozygous for the same deleterious *CNGB3* mutation. Given the progression of the disease in (V:5) to complete achromatopsia in the later follow-up examination and the difference in age between (V:2) and (V:5) at the time of the 1956 Fuur expedition (9 years versus 18 years), the phenotypic difference during the early examinations may simply reflect the natural course of disease for this specific *CNGB3* frameshift mutation. However, the potential and partially unknown effects of more distant regulatory elements and epigenetic modifications might also have contributed to the inter-individual difference in the ‘slope’ of progression.

In conclusion, re-examinations of members of the Fuur family confirmed a diagnosis of complete congenital achromatopsia. With respect to the mainland family, the visual condition of the elder brother was unchanged during 36 years of observation, in the middle brother it had progressed into complete achromatopsia, while the youngest brother showed a deviating phenotype with low vision and deuteranopia. The molecular genetic investigation uncovered a shared genotype in the two elder brothers, its exclusion in the youngest brother with low vision and deuteranopia adds a novel mystery to the story of the Fuur achromats. Today the phenotype discordance in the two brothers published by Francheschetti [5] and Jaeger [10] would not give rise to any wonder.

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