Genetics of microphthalmos

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Abstract

This is a survey of the genetics of microphthalmos and the heritable syndromes in which microphthalmos occurs. New syndromes are delineated such as the autosomal dominant anophthalmos-microphthalmos-coloboma syndrome, the autosomal dominant microphthalmos, microcephaly, lacunar retinal atrophy syndrome, the autosomal recessive anophthalmos-microphthalmos-coloboma syndrome, the autosomal recessive syndrome with anophthalmos or microphthalmos and genital malformations, and the autosomal recessive syndrome with microphthalmos, microcephaly and retinal falciform folds. Nanophthalmos is described as a poorly defined phenotype and rejected as a genotype. Several other genetic entities with microphthalmos are reviewed and recent descriptions are surveyed.

Introduction

Microphthalmos is a developmental arrest of ocular growth and should be differentiated from secondary shrinkage. Genetically, microphthalmos and anophthalmos can be considered together because both phenotypes may occur in the same family, and because all clinical cases of anophthalmos must be considered as extreme microphthalmos.

Primary anophthalmos is a lack of prospective ocular primordia; the prospective neuro-retinal cells arise from a single central eye field (193, 200) which divides, whereafter the ocular primordial cells migrate laterally. A defect of presumptive neuro-retinal cells in this single eye field will lead to anophthalmos or microphthalmos in a cyclopian orbit, and this is associated with such serious malformations of the brain that it is prohibitive for postnatal and even usually for continued embryonic life.

Microphthalmos and microcornea are often not differentiated in pediatric descriptions, and there are syndromes which may present with either malformation in members of the same family. Genetically, therefore it is practical discussing both phenotypes together.

If microphthalmos is unassociated with other ocular malformations, it is termed nanophthalmos, but microphthalmos may also be associated with ordinary or cystic colobomata. Nanophthalmos and colobomatous microphthalmos have repeatedly been described in members of the same families (Figs. 1 and 3), thus the terms reflect the phenotypes rather than the expressions of particular genotypes.

In an ophthalmic out-patient clinic 0.02-0.15 per cent (95, 122) of the patients have microphthalmos, and this is similar to the prevalence of microphthalmos observed among neonates (80). Among
2557 blind adults Lindstedt (132) found 1.9 per cent with microphthalmos, and among blind children in the Netherlands, Belgium, Norway, Sweden and Denmark 5 to 10 per cent had malformations, i.e. anophthalmos, microphthalmos, colobomata or multiple ocular malformations (175).

Most cases of microphthalmos are sporadic (66, 183, 210), but many are heritable. The genetic cases may be chromosomal and Medelian; only the latter will be discussed in the following.

**Autosomal dominant traits with microphthalmos**

**Autosomal dominant anophthalmos – microphthalmos – coloboma syndrome**

Anophthalmos, microphthalmos and coloboma may be expressions of the same autosomal dominant gene. In such families, the affected individuals are often but not invariably mentally retarded. Otherwise they present no systemic signs. Typical pedigrees have been described by Francois (59), Romano (170), and Hussels (102) as shown in Fig. 1. The trait is undoubtedly very rare.

**Autosomal dominant microphthalmos, microcornea and cataract**

This syndrome has been described in a few families (26, 68, 93, 210); it is often associated with mental retardation. It is uncertain if the individuals with microcornea carry the same mutation as those with microphthalmos or not.

In the family described by Adams and Nance (1), microphthalmos and cataract were associated with *renal stones* and *hyperglycinuria*. The authors speculated that this was either due to chance associations or to a chromosomal aberration which could not be demonstrated by the methods available at the time.

**Microcornea, cataract and coloboma**

This association was described in several genera-

![Autosomal Dominant Anophthalmos-Microphthalmos-Coloboma Syndrome](image)

**Oculo-dento-digital syndrome (oculo-dento-osseous syndrome)**

This syndrome is the autosomal dominant trait with microphthalmos which has been described in the largest number of patients. It was first observed by Lohmann (134), and Meyer-Schwickerath, Grüterich and Weyers (147) collected a number of cases and delineated the syndrome. In 1969, Reisner et al (169) analysed 43 cases described until then, and Judisch et al (119) gave a brilliant survey of 41 accepted cases. Only a few more have been described (13, 52, 54, 89, 188, 191, 208).

Microcornea is common in this syndrome (119), but anophthalmos (54) and coloboma (124) have also been described. The palpebral fissure is small (below 30 mm). Heterochromia of the irides, persistent pupillary membrane and poorly defined collarette were seen in some patients.

Glaucoma (48, 120, 147, 188) may be observed in early adult age, and congenital glaucoma has also been described (120). The fundus has mostly been described as normal, but Judisch et al. (119) found an excessive number of vessels crossing the disc and Thodén et al. (19) observed an infant with the syndrome, who had a grey disc and attenuated...