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# Allan-Herndon Syndrome. I. Clinical Studies

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## Summary

**A large family with X-linked mental retardation, originally reported in 1944 by Allan, Herndon, and Dudley, has been reinvestigated. Twenty-nine males have been affected in seven generations. Clinical features include severe mental retardation, dysarthria, ataxia, athetoid movements, muscle hypoplasia, and spastic paraplegia with hyperreflexia, clonus, and Babinski reflexes. The facies appear elongated with normal head circumference, bitemporal narrowing, and large, simple ears. Contractures develop at both small and large joints. Statural growth is normal and macroorchidism does not occur. Longevity is not impaired. High-resolution chromosomes, serum creatine kinase, and amino acids are normal. This condition, termed the Allan-Herndon syndrome, appears distinct from other X-linked disorders having mental retardation, muscle hypoplasia, and spastic paraplegia.**

## Introduction

A 6-generation family in which males were affected with mental retardation was reported in 1944 by the pioneer geneticists William Allan and Nash Herndon and their social worker Florence Dudley (Allan et al. 1944). The condition, the first reported to describe "sex-linked" mental retardation, affected 24 males. Affected males had hypotonia, areflexia, muscle atrophy, and microcephaly in addition to the mental impairment. Although no reports of the Allan-Herndon syndrome have appeared in the literature since the original publication, numerous reports of families with X-linked spastic paraplegia, spinocerebellar ataxia, or cerebellar degeneration and mental retardation are available, some of which have features present in this entity (Malamud and Cohen 1958; Baar and Gabriel 1966; Bundey and Griffiths 1977; Davis et al. 1981; Apak et al. 1989).

The family has been reinvestigated, now 50 years after the initial field studies. Three subsequent generations have been added to the pedigree and five additional affected males have been identified. The youngest affected member is age 25 years and the oldest 71 years. The natural history can now be documented and the phenotype revised.

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## Case Reports

Figure 1 shows the revised pedigree. Twenty-nine affected males have been identified in 7 generations. No affected male has been detected in the two most recent generations (generation IX is not shown on the pedigree). Each of the 13 affected persons who are alive has been examined (figs. 2, 3). Their features will be briefly summarized below and given individually in table 1. One representative case (VI-27) will be presented in greater detail.

Although some measure of variability can be seen among the affected males, a relatively consistent pattern of findings distinguishes this syndrome. No history of pregnancy or perinatal difficulties has been elicited from the mothers of affected males. Fetal movement during pregnancy is not diminished. Most affected males were born at home and were estimated to have normal birth weights. Birth weights were recorded in only two instances: 3.7 kg for VI-37 and 4.5 kg for VII-9. The disorder becomes obvious during the first year as motor milestones in affected males lag behind those of their age-mates and unaffected siblings. The

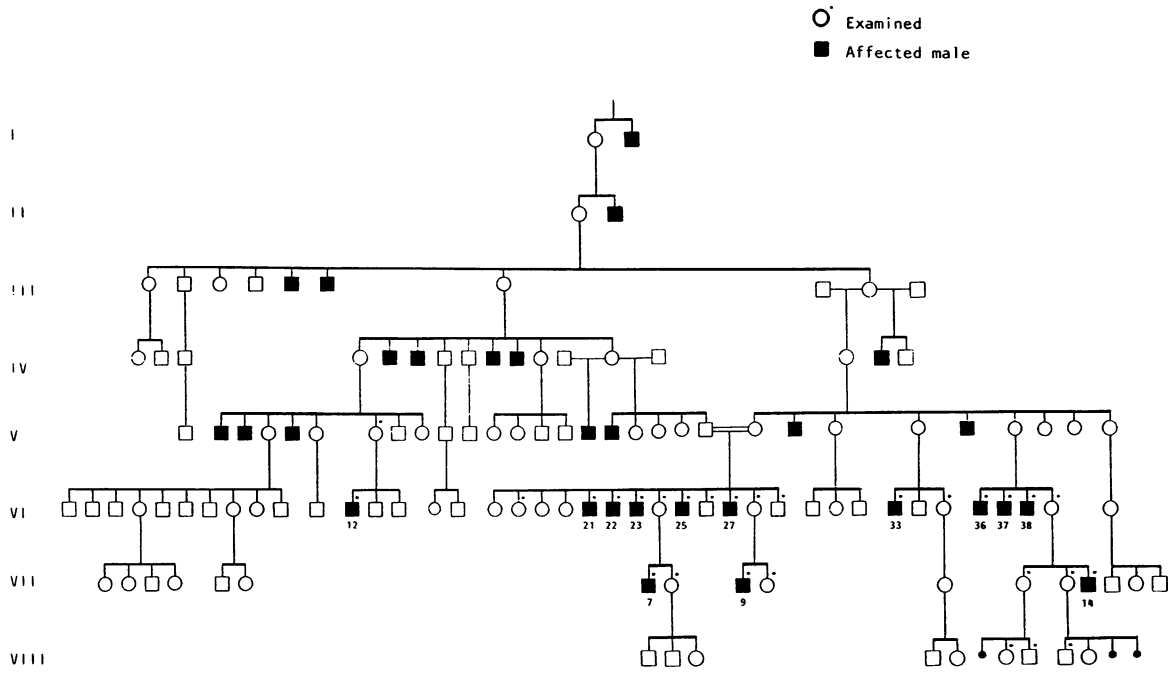


**Figure 1** Revised pedigree of family with the Allan-Herndon syndrome. Five affected males in 2 generations have been added since the original publication.

profound motor weakness appears to prevent development of motor skills on a timely basis. Earliest walking occurs at about 3 years of age, some being delayed well beyond that age, and some affected males never walk. Attempts at speech begin at about the same age, that is, 3–4 years, with speech being indistinct. Childhood stature progresses at a normal rate, but general muscular hypoplasia causes most of the affected to appear quite asthenic (fig. 3). Adult height appears comparable to or greater than that of unaffected brothers. Hand and palm lengths are normal (table 1).

All muscles of the neck, trunk, and limbs appear underdeveloped and weak, causing difficulties in ambulation and posture. Neck drop is a frequent sign, this apparently due to tiring of the neck muscles under the weight of the head, and provides the basis for the family term "limber neck," given to affected boys. Deep tendon reflexes are increased in the lower extremities, and ankle clonus or extensor plantar responses are usually present. Some of the affected males acquire clubfoot or joint contractures. In adult life those who retain ambulation do so with difficulty, walking with an unsteady and shuffling gait, generally requiring assistance. Muscle pseudohypertrophy does not occur, nor do affected males utilize Gowers maneuvers typical of muscular dystrophy patients having girdle weakness.

The facies are not uniform, although in most cases the cranium shows bitemporal narrowing and the facies is elongated (fig. 2). The pinnae are cupped or simple in formation in several. Vision and hearing appears unimpaired. Fundiscopic examination is normal. Nystagmus is not present. Puberty occurs at the expected time without evidence of hypogonadism, macroorchidism, or other abnormality of the genitalia. Structural malformations do not occur as a part of the syndrome. No affected male has reproduced. Two have adult-onset diabetes mellitus, but otherwise affected males are free of chronic illness. Postmortem examination has not been conducted on any affected male.

High resolution chromosome analyses (VI-21, VI-22, VI-23, VI-25, VI-27, VI-33, VI-38, VII-14), fragile-site analysis (VI-23, VI-33, VI-38), plasma amino acids and organic acids (VI-27, VI-12), and serum creatine phosphokinase level (VI-21, VI-22, VI-23, VI-25, VI-27, VI-33, VI-36, VI-38, VII-7, VII-14) were all normal.

Female carriers show no evidence of mental retardation, muscle weakness, cerebellar dysfunction, spasticity, or any of the other features of their affected male relatives. Unaffected brothers appear of normal intellect but have not had formal testing.

Case VI-27 was the 12th of 14 children born to second cousins and the fifth male in this sibship to have

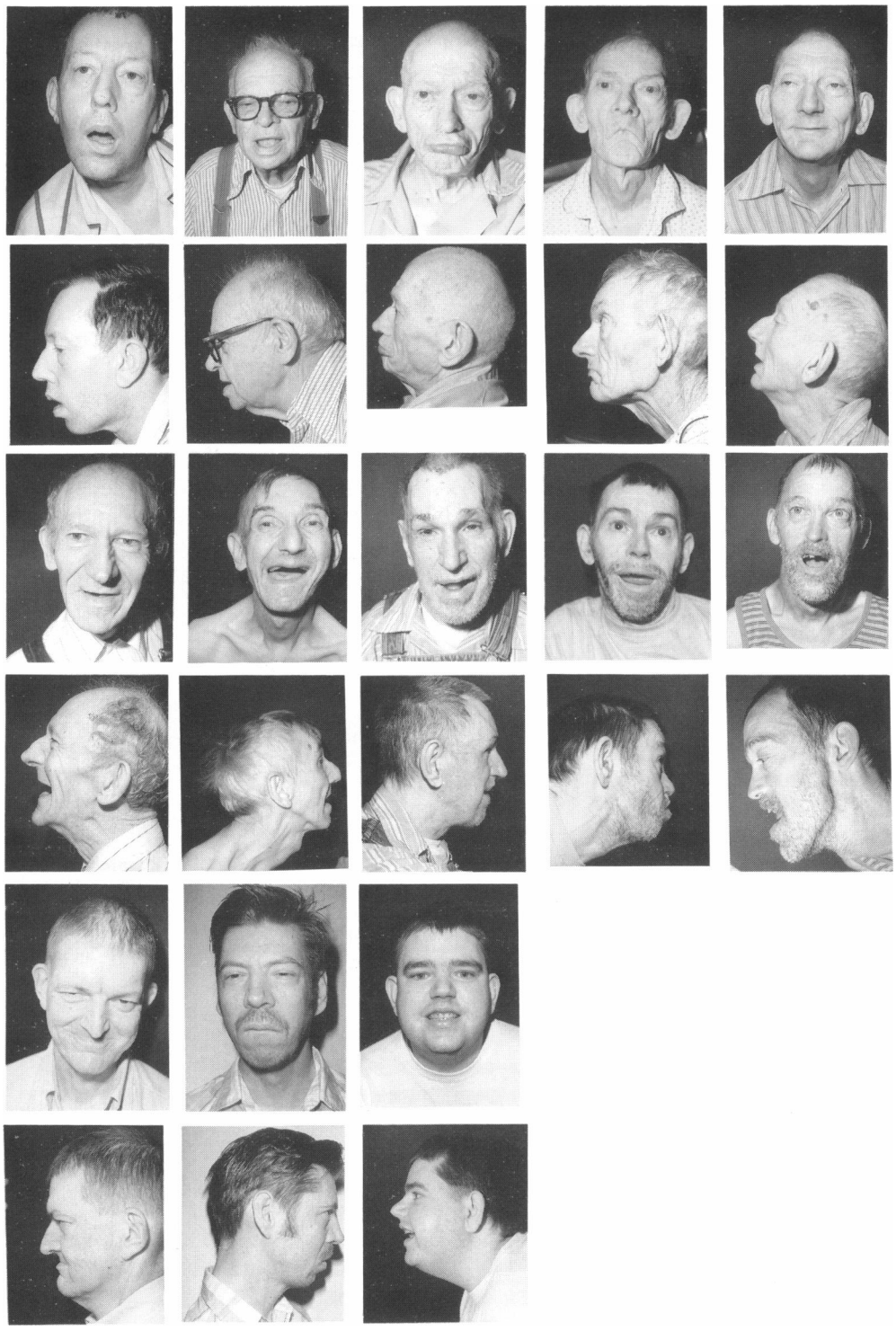

**Figure 2** Facial features in 13 affected males. *Top two rows;* VI-12, VI-21, VI-22, VI-23, VI-25; *middle two rows;* VI-27, VI-33, VI-36, VI-37, VI-38; *bottom two rows;* VII-7, VII-9, VII-14. Note myopathic features in VI-12. Several males have elongation of the face with bitemporal narrowing, central balding, and large ears.

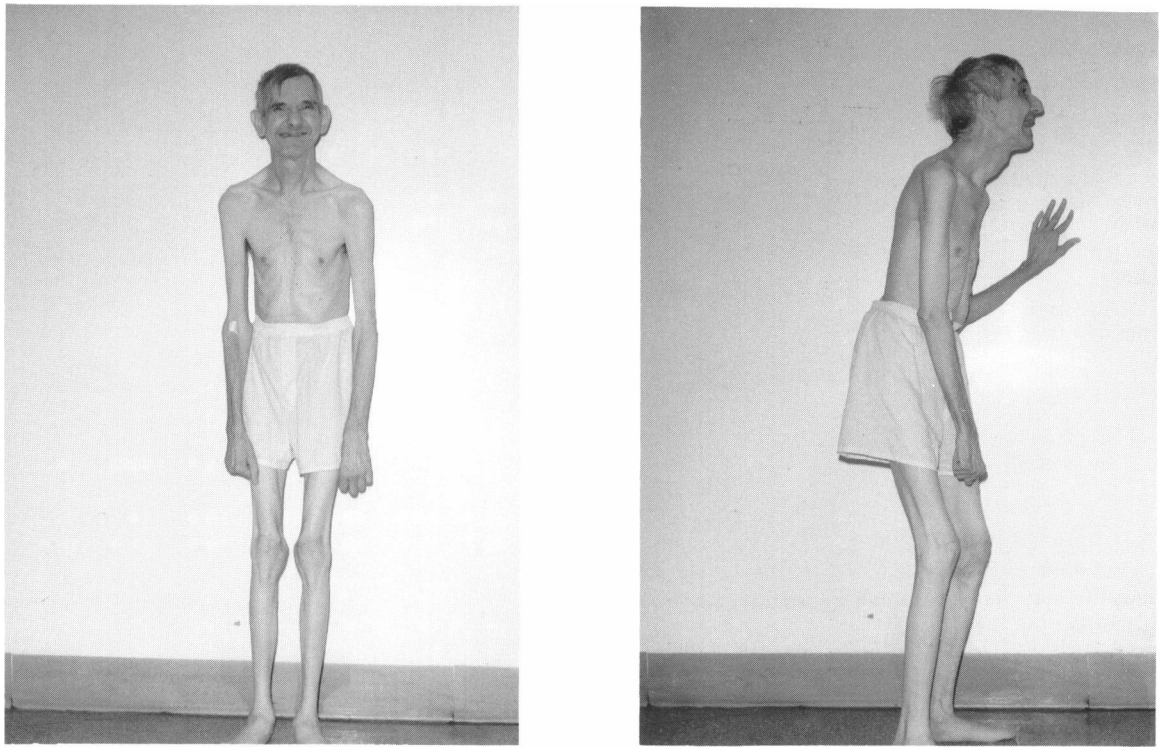

**Figure 3** Full frontal and side views of VI-33 showing marked muscle hypoplasia

mental retardation. One sister was stillborn and one presumably normal brother died of meningitis at age 14 mo. The father died at age 91 of renal failure and the mother at age 49 of uterine cancer.

Details of the pregnancy, birth, and neonatal period are not known. He was born at home, having unknown weight. Precise early developmental milestones cannot be given, but were globally delayed. He began walking and talking after age 4, always ambulated with some difficulty, and his speech was largely unintelligible. He never attended school and was institutionalized in early adult life.

At age 58 years, VI-27 could ambulate for short distances but had ataxic gait. He appeared normally developed but was quite asthenic. He had normal head circumference (56.8 cm), height (183 cm with stooped posture) and weight (47.7 kg). Craniofacial features included elongation of the face, prominent mandible, central balding, and cupped pinnae measuring 7.2 cm (fig. 2). Fundiscopic examination was normal. The chest was narrow with mild pectus excavatum and scoliosis. A murmur of mitral insufficiency was present. The proximal interphalangeal joints of the fingers were stiff with contractures of the fifth fingers. The elbows were hyperextensible. Neurological findings included mental impairment, drooling, severe dysarthria, and choreoathetoid movements of the face, trunk, and extremities. Deep tendon reflexes were exaggerated at the knees and clonus was present bilaterally. Genitalia appeared normal with testicular volumes of 22 ml (left) and 25 ml (right).

Peripheral nerve conduction velocity was mildly impaired (peroneal nerve) and some spontaneous motor potentials suggested a denervation process. Magnetic resonance imaging of the brain showed prominence of the cortical sulci, mild dilation of the ventricular system, and multiple foci of abnormal signal in the periventricular and deep white matter, all findings commonly seen in older patients. A muscle biopsy showed no myopathic, neuropathic, or inflammatory changes. Intelligence testing resulted in a ratio IQ of 19 (Stanford-Binet).

Features of the other 12 affected males are given in table 1. VI-21 and VII-7 represent the least severe end of the spectrum of involvement. They do not show muscle hypoplasia, clonus or ataxia, and have achieved bet-

**Table 1**

**Clinical Features in Patients with the Allan-Herndon Syndrome**

| | Patient | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VI-12 | VI-21 | VI-22 | VI-23 | VI-25 | VI-27 | VI-33 | VI-36 | VI-37 | VI-38 | VII-7 | VII-9 | VII-14 |
| Age | 49 | 71 | 68 | 67 | 61 | 58 | 65 | 57 | 52 | 50 | 45 | 39 | 25 |
| Adult height (cm) | 178 | 173 | ...[a] | ...[a] | ...[a] | 183 | 175 | 171 | ...[a] | ...[a] | 185 | 193 | ...[a] |
| Ambulatory | − | + | − | − | − | + | + | + | − | + | + | + | − |
| Craniofacies: | | | | | | | | | | | | | |
| Head circumference (cm) | 58 | 57 | 54 | 55.5 | 58.5 | 57 | 56.5 | 56 | 54.5 | 55 | 57.5 | 58.5 | 57 |
| Biotemporal narrowing | + | − | + | + | + | − | + | + | + | + | − | − | − |
| Long face | + | − | + | + | − | + | − | + | − | − | − | + | − |
| Frontal balding | + | + | + | + | + | + | − | + | + | + | − | − | − |
| Midface hypoplasia | + | − | − | + | + | − | − | + | + | + | + | − | − |
| Cupped/simple pinnae | − | − | + | + | + | + | − | − | − | − | + | − | − |
| Pinna diameter (cm) | 7.7 | 7.8 | 7.7 | 7.0 | 7.8 | 7.2 | 7.3 | 8.1 | 6.9 | 6.9 | ONM | 8.2 | 7.4 |
| Skeletal: | | | | | | | | | | | | | |
| Hand length (cm) | 18 | 19.3 | 17.2 | 17.4 | 18.4 | 18.3 | 19.8 | 18.9 | 19.4 | 18.8 | 18.1 | 23 | 18.8 |
| Palm length (cm) | 10.6 | 11.4 | 9.9 | 10.1 | 10.7 | 10.5 | 11.0 | 10.7 | 11.5 | 10.9 | 10.8 | 10.8 | 10.6 |
| Stiff digits/contractures | + | + | − | − | − | + | − | − | ONM | − | − | − | − |
| Horizontal palmar creases | − | − | + | − | − | − | + | − | − | + | − | − | + |
| Narrow/malformed chest | − | − | − | + | + | + | + | + | + | + | − | + | − |
| Scoliosis | − | − | − | − | − | + | − | − | + | − | − | − | − |
| Large joint contractures | + | − | − | + | − | − | − | + | + | + | − | + | + |
| Testicular volume (cc): | | | | | | | | | | | | | |
| Left | ONM | 17 | 18 | 11 | 35 | 22 | 18 | 25 | ONM | 19 | 21 | ONM | ONM |
| Right | ONM | 17 | 15 | 24 | 33 | 25 | 26 | 21 | ONM | 25 | 25 | ONM | ONM |
| Neuromuscular: | | | | | | | | | | | | | |
| Nystagmus | − | − | − | − | − | − | − | ONM | − | − | − | − | ONM |
| Dysarthria | + | − | + | + | + | + | + | + | + | + | + | + | + |
| Ataxia | + | − | + | + | + | + | + | + | + | + | − | + | + |
| Athetosis | − | − | + | + | + | + | + | + | + | + | − | + | + |
| Muscle hypoplasia | − | − | + | + | + | + | + | + | + | + | − | + | − |
| Exaggerated reflexes | + | − | + | + | + | + | + | + | + | + | + | + | + |
| Clonus/Babinski | + | − | + | + | + | + | + | + | ONM | + | − | + | ...[a] |
| IQ (Stanford-Binet) | ONM | 30 | 23 | 13 | 20 | 19 | 20 | ONM | 26 | ONM | 34 | ONM | ONM |

NOTE.—ONM = observation not made.

[a] Accurate assessment not possible because of contractures.

ter speech, ambulation, social skills, and IQ scores (30 and 34, respectively) than the other affected relatives. VI-27, VI-33, VI-36, VI-38, and VII-9 retain the ability to walk but do so with great difficulty, being quite unsteady and generally requiring assistance. Excepting VI-21, all have increased deep tendon reflexes of the lower extremities and most have clonus and/or extensor plantar responses. VI-12 and VII-9 appear myopathic, with elongation of the facies, frontal balding, and open mouth. All have normal head sizes, stature, and sexual maturation. VII-14 alone has obesity.

## Discussion

An excess of males has been consistently found in studies of mentally retarded persons whether based on public school, community day school, or institutionalized samples. Males outnumber females in institutions and community day programs in South Carolina, sex ratios being 1.31 and 1.23, respectively (M. Moody, personal communication). Similarly, three studies with almost complete ascertainment for severe mental retardation yielded male:female sex ratios of 1.27 (Birch et al. 1970), 1.30 (Lewis 1929), and 1.43 (Wing 1971).

Complete ascertainment of persons with mild retardation has been more difficult because they require services less often than severe retardates. Moser and Wolf (1971) reported a ratio of 1.49 among residents of Fernald State School with IQ's above 50. R. J. Simensen (unpublished data) found sex ratios among students

**Table 2**

**X-linked Mental Retardation Syndromes with Spastic Paraplegia and Ataxia**

| McKusick Number | Syndrome | Spastic Paraplegia | Ataxia |
|---|---|---|---|
| 30010 ..... | Adrenoleukodystrophy | + | + |
| 30179 ..... | Ataxia and deafness | – | + |
| 30270 ..... | Scholz cerebral sclerosis | + | – |
| 30335[a] ..... | Clasp thumb | + | – |
| 30700 ..... | Aqueductal stenosis | + | – |
| 30800 ..... | Lesch-Nyhan | + | – |
| 30885 ..... | Laryngeal abductor paralysis | – | + |
| 30893 ..... | Leigh | + | ± |
| 30895 ..... | Lesch-Nyhan, normal HPRT | + | – |
| 30925[a] ..... | MASA | + | – |
| 30940 ..... | Menke | + | + |
| 30956 ..... | Fitzsimmons mental retardation | + | – |
| 30958 ..... | Smith-Fineman-Myers mental retardation | ± | – |
| 30960[b] ..... | Allan-Herndon | + | + |
| 30964[b] ..... | Davis mental retardation | + | |
| 30980 ..... | Lenz microphthalmia | + | – |
| 31105 ..... | Optic atrophy, non-Leber | + | + |
| 31125 ..... | Ornithine transcarbamylase deficiency | + | + |
| 31140 ..... | Paine mental retardation | + | – |
| 31208 ..... | Pelizaeus-Merzbacher | + | + |
| 31275 ..... | Rett | + | + |
| 31284 ..... | Schimke mental retardation | + | – |
| 31289 ..... | Spastic athetoid paraplegia | + | + |
| 31290 ..... | Spastic paraplegia, complicated | + | + |
| 31291 ..... | Spastic paraparesis and deafness | + | – |

NOTE.—McKusick numbers with the same superscript letter may represent the same entity; see Discussion. ± = Present in some but not in all.

in educable mentally handicapped classes (IQ 50–70) of 1.32 (Florida) and 1.30 (Illinois), and 1.23 (South Carolina). These excesses of males have been attributed largely to males' being hemizygous for X-linked genes whereas carrier females are generally spared by the presence of the normal allele on their second X chromosome.

Seventy-three distinctive conditions with mental retardation have been delineated which are determined by mutations on the X chromosome (McKusick 1988). Spastic paraplegia occurs as a feature in one-third of these entities, and ataxia also occurs frequently (table 2). Considerable variability in corticospinal tract, spinocerebellar, and cerebellar signs may be found among these disorders and even within the same family. Twenty-two X-linked disorders with mental retardation have now been regionally mapped and include dysmorphic, metabolic, and fragile-site syndromes (fig. 4). In addition, numerous families with mental retardation limited to males but without specific phenotypic features have been recognized. These have collectively been termed "nonspecific" X-linked mental retardation.

Mental retardation and spastic paraplegia with or without cerebellar signs may be found in a number of X-linked disorders. The list of these disorders (table 2) must be viewed as tentative since none can be clearly distinguished on the basis of clinical or laboratory findings. An underlying metabolic disturbance can be demonstrated in several of these syndromes, including adrenoleukodystrophy, Lesch-Nyhan syndrome, Menkes syndrome, Leigh syndrome, and ornithine transcarbamylase deficiency. Distinctive clinical findings which help in differential diagnosis occur in several others including aqueductal stenosis, laryngeal abductor paralysis, Lenz microphthalmia, Fitzsimmons mental retardation, Rett syndrome, and non-Leber optic atrophy.

Recent molecular studies have shown three of the X-linked mental retardation disorders listed separately in table 2 to be linked to the same Xq28 DNA markers (Kenwrick et al. 1986; Winter et al. 1989). These three,

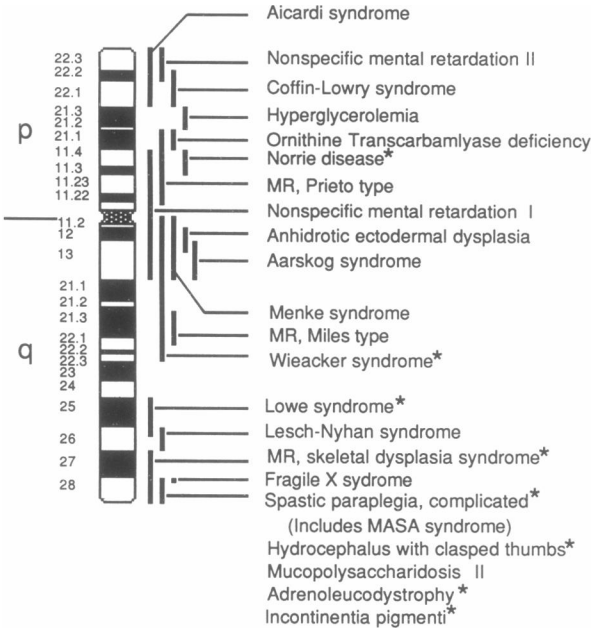


**Figure 4** Map of the X chromosome showing regional localization of conditions with mental retardation. Asterisks indicate those loci assigned through linkage analysis with lod score of 3 or greater.

mental retardation with clasp thumb, complicated spastic paraplegia, and MASA syndrome (mental retardation, aphasia, shuffling gait, and adducted thumbs) may thus represent allelic conditions, closely linked entities, or possibly the same entity.

The first fragile-X-negative family determined to have X-linked mental retardation was the family herein described, reported by Allan, Herndon, and Dudley in 1944. No other reports since have claimed to describe the same syndrome. Unreported families with similar features have been recognized in New York and Minnesota (J. A. Edwards, personal communication; R. A. Gorlin, personal communication). A family reported in abstract form by Davis et al. (1981) may represent the Allan-Herndon syndrome. Nine males in this family had muscle wasting, dysarthria, hyperreflexia, clonus, spastic gait, scoliosis, equinovarus deformity, and mental retardation of variable degree. The family reported as pedigree 22 by Bundey and Griffiths (1977) is similar.

The X-linked spastic paraplegia reported by Baar and Gabriel (1966) differs in having nystagmus as a prominent feature. Although patient III-16 of Wieacker et al. (1985) has similar facial features to several of those reported herein, he appears quite different otherwise, having club foot present at birth, defective ocular movements, milder mental defect, and normal deep tendon reflexes. Other families reported by Johnston and McKusick (1962), Zatz et al. (1976), and Thurmon et al. (1971) have spasticity but normal or near-normal intelligence. Families reported by Malamud and Cohen (1958), Schmidley et al. (1987), and Lutz et al. (1989) have greater cerebellar involvement.

Based on reevaluation of the original family, the Allan-Herndon syndrome is characterized by severe mental deficit, dysarthria, ataxia, athetosis, generalized muscle hypoplasia, hyperreflexia, and the craniofacial features of bitemporal narrowing, large ears, and narrow face. Affected males have normal birth measurements, statural growth, cranial circumference, and testicular measurements. They do not have congenital malformations. Longevity does not appear to be impaired. Five affected males are currently over 60 years of age.

The Allan-Herndon syndrome appears to be a distinctive X-linked mental retardation syndrome. With the exception of families reported by Bundey and Griffiths (1977) and Davis et al. (1981), each of the many families with X-linked mental retardation in the literature appears significantly different from the Allan-Herndon syndrome. Many of these may be distinguished through clinical or laboratory studies. Linkage studies and resolution at the molecular level will be required to determine if any of these conditions represent phenotypic variants with the same mutation, allelic mutations, or components of a shared contiguous gene complex.

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