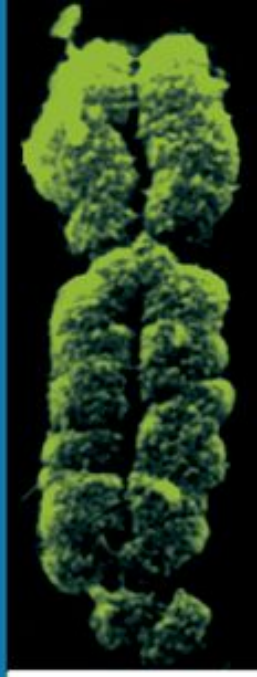
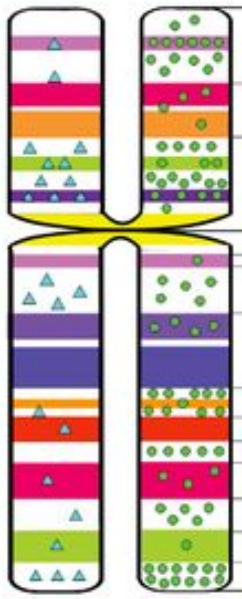
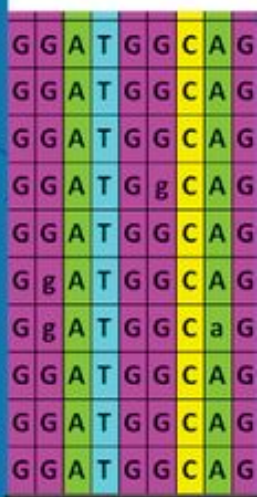
SECOND EDITION

ATLAS OF X-Linked Intellectual Disability Syndromes







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OXFORD

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This Atlas is dedicated to all persons with X-linked intellectual disability, to their families, to the physicians that provide medical care, to the scientists that seek to understand the underlying biology, and to the memory of Ethan Francis Schwartz 1996–1998.

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FOREWORD

The Greenwood Genetic Center in South Carolina was established in 1974 through the efforts of Roger Stevenson and his associates to provide a diagnostic and assessment service for the state for those with intellectual disability (ID). During the eighties and nineties the major contribution of X-linked genes to ID became accepted. This stimulated the Center to publish in 2000 a now classic book entitled *X-Linked Mental Retardation*. The first half gave an account of the history of X-linked ID and the second half was an atlas with pictures and clinical details of the affected males from published families. It included 125 different syndromes. In many, linkage studies had identified the gene location but in only very few had the responsible gene mutation been identified.

This second edition of the *Atlas* is a marvelous 10-year update. It will be essential not only as a reference book for medical geneticists but also for molecular laboratories providing a gene screening service. Over the past ten years since the publication of the previous edition, around 100 genes and their mutations have been identified in those with clinical syndromes and over 33 in 95 families with nonsyndromic XLID. Some clinical diagnoses have now been recognized as different manifestations of the same gene as in the 24 base-pair duplications in the *ARX* gene. There has also been a merging of the syndromic with the non-syndromic, as families have been found in which different affected members may have features of either syndromic or non-syndromic ID but carry the same mutation.

Atlas of X-Linked Intellectual Disability Syndromes will have two main functions. The first is as a help in clinical diagnosis when the facial gestalt or a cluster of clinical features brings a particular diagnosis to mind. A quick look at the atlas will help confirm this suspicion and the clinician know whether the gene has been identified.

The second, more important function is just becoming apparent. In the immediate past if one made a clinical diagnosis of an X-linked ID condition and if the gene had been identified, the next step was to look for a laboratory willing to test for that mutation. Now the scene has been reversed. In investigating a singleton male with ID or someone from a family that might have a mutation in a gene coded on the X, one can order an X gene screen covering most of the a multigene sequencing panel that includes all genes associated with XLID. This is a service now offered not on by Greenwood Genetic Center but is also available in through other laboratories. A result comes back reporting a mutation in gene *ABC*. This atlas can provide both the information of the clinical features associated with mutations in that gene with some idea of the prognosis and references to more detailed clinical reports. The classical sequence of clinical diagnosis to causal mutation has given way to causal mutation to clinical diagnosis.

This will lead to major changes in clinical practice. There will be far less discussion, in the clinic and at meetings as to whether a particular set of clinical findings fits in with one syndrome as opposed to another. The laboratory will often be able to settle the matter. All undiagnosed males with ID will have a molecular karyotype and, if necessary, will be followed by a screen of the genes on the X chromosome, soon to be followed by looking for de novo mutations. Is this the death knell of the clinical dysmorphologist? Lay and professional support groups will be known more by their mutations than by their eponymous or anatomical syndromes as is happening with chromosomal disorders. The Internet will provide increasingly accurate clinical and molecular data.

Molecular testing is rapidly becoming less expensive. This will allow the introduction of pre-pregnancy testing for carriers of X-linked ID to be added to the routine screenings. This *Atlas of X-Linked Intellectual Disability Syndromes* will be invaluable in interpreting the findings.

The authors are to be congratulated on producing a major new reference similar in importance today as was the publication of Dave Smith's *Recognizable Patterns of Human Malformations* in the sixties. Information in this field continues to accumulate rapidly and we look forward to the next edition in less than 10 year's time. This atlas is one more step in the mission of the Greenwood Genetic Center of having all babies born free of physical and mental disabilities.

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PREFACE

In the early days of human development, the brain dominates the embryological landscape. As other organ systems develop and the fetus grows, the brain becomes less formidable anatomically, but progressively more complex functionally. Soon after postnatal life begins, it engages the environment and issues responses that bind the child to parents and to others. It enables the acquisition of skills that serve as benchmarks of developmental progress. Ultimately, the brain defines the essence of human existence through the control of thought processes, neurological function, and behavior.

A certain fragility of the developing brain is suggested by the high prevalence in the population of significant impairment of cognitive and adaptive performance. Such impairments may be associated with faulty formation or function of the brain, occur in one to three percent of the population, and are considered collectively under the general term intellectual disability. The high frequency with which developmental failure of the brain occurs is found in no other organ system. The developing brain may, thus, be easily damaged or minor damage may be more readily expressed. Alternatively, other organ systems may have structural or functional redundancy that gives greater capacity in reserve.

Intellectual disability – significant impairment of cognitive and adaptive functions – exists as a human phenomenon with numerous dimensions. For the affected individual, it represents a cloak that limits capacity to learn, ability for expression, freedom of movement, and achievement of goals. For society, it represents a disability characterized by reduced productivity, some measure of dependency, and vulnerability to discrimination and exploitation. For public health, it is a common abnormality, one that is distributed throughout all strata of the population, and imposes a costly and lifelong burden. For medicine, intellectual disability represents an aberration in the formation and/or function of the central nervous system that demands evaluation and explanation.

Partition of intellectual disability by cause is informative on several counts. Scientifically, it confirms that the developing brain is susceptible to a wide variety of insults including faulty genetic instructions, environmental influences, and a combination of these two forces. Only with recognition of the causes can specific strategies for treatment and prevention be devised. From a practical clinical standpoint, knowledge of causes gives the clinician a basis to judiciously select diagnostic tests, predict natural history, calculate recurrence risks, direct counseling, and make reasonable medical and educational plans.

A pervasive finding among persons with intellectual disability has been the excess of males. In most populations, the excess is about 20–40%. The biological inequity between males and females conferred by the different number of sex chromosomes has been considered primarily responsible for the excess. Accepting a male excess of 30%, one would estimate that XLID constitutes one of the most common causal categories of intellectual disability, equaling that of chromosome aberrations. However, the current ability to identify intellectual disability due to X-linked genes in clinical populations accounts for only a fraction of this number.

X-linked intellectual disability has been divided into two broad categories, syndromal and nonsyndromal (or nonspecific). In syndromal X-linked intellectual disability, somatic, neurologic, behavioral, or metabolic abnormalities accompany the intellectual disability and often constitute a recognizable pattern. In nonsyndromal X-linked intellectual disability, males have no somatic, neurologic, behavioral, or metabolic findings that distinguish them from nonaffected brothers or from other males with intellectual disability.

A large number of families with syndromal and nonsyndromal forms of XLID have been reported, primarily during the past 50 years. Although there have been recent advances to confirm diagnoses with biochemical or molecular testing, the clues to identification of most XLID syndromes come from the family history and phenotype. This *Atlas of X-Linked Intellectual Disability* is intended to provide the clinicians, scientists, and students with a resource to differentiate the various types of XLID on the basis of craniofacial or other somatic findings, neurologic signs or symptoms, behavioral manifestations, brain imaging, and laboratory testing. Separate genes exist for many, but not all, of the 150 syndromal forms of XLID.

Delineation of the various forms of XLID has been possible only through the contributions of affected families

and their physicians. To them, we are indebted and to them we dedicate this monograph. Researchers worldwide have followed up the clinical observations with systematic biological investigations, including a wide variety of imaging, histologic, molecular and cytogenetic studies, which have permitted delineation of the phenotype and localization of the majority of the X-linked intellectual disability syndromes. The responsible genes have now been identified in two-thirds of the syndromes.

Prior to publication of *X-Linked Mental Retardation* in 2000, the laboratory approach to gene localization and identification was limited to pursuit of genes where the gene products were known (enzymes in all cases: *HPRT*, *PGK1*, *OTC*, and *PHDA1*), exploration of chromosome rearrangements (predominately X-autosome translocations), and linkage analysis in large families in which XLID appeared to segregate. Since that time, the study of breakpoints in chromosome rearrangements and linkage analysis coupled with candidate gene testing, have continued to be the most productive means of gene identification. Brute force sequencing of the X chromosome and genomic microarrays for copy number variants coupled with candidate gene testing, have been added to these technologies in recent years. Prior to 2000, 30 XLID genes had been identified; since then an additional 72 XLID genes have been identified. Among families suspected to have XLID, 40–50% of the responsible mutations can now be identified with the most commonly affected genes, besides *FMR1*, being *ARX* (5–6%), and *MECP2*, *OPHN1*, *PQBP1*, and *KDM5C* (each 1–4%). Mutations are detected in a much lower percentage of sporadic males with ID.

Segmental duplications involving one or more genes on the X chromosome have been associated with intellectual disability. The most common of the segmental duplications involves the *PLP1* gene at Xq22 and is responsible for the majority of cases of Pelizaeus–Merzbacher disease (Mimault et al. 1999). A second important duplication occurs in Xq28 and includes *MECP2* with or without adjacent genes. The phenotype includes severe intellectual disability (sometimes with co-occurring autism or autistic manifestations), hypotonia, absent or limited speech, absent or limited ambulation, spasticity, seizures, and recurrent respiratory infections (Van Esch et al. 2005, Friez et al. 2006). In some cases of X chromosome segmental duplications, it is unclear whether the whole gene duplication, partial duplication of adjacent gene or other position effect is most important in the causation of ID. In many cases of clinically important segmental duplication of the X chromosome, marked skewing of X-inactivation has been documented in carrier females.

The clinical re-evaluation of families with XLID previously reported, observations in more recently ascertained families, and the incorporation of molecular technologies in diagnosis have resulted in lumping, splitting and reclassification of a number of XLID. With the variability and imprecision with which clinical evaluations are carried out, it is inevitable that some individuals with X-linked intellectual disability will be incorrectly included in existing diagnostic categories while others will be incorrectly excluded. The extent to which individuals/families can be evaluated is dependent on the setting, access to historical information, availability and ages of affected and nonaffected family members, and the experience and expertise of the observers. Differences in phenotype can result from mutations in different domains of a gene and by contributions from the balance of the genome. The identification of many causative XLID genes has provided the opportunity to compensate for some of these variables, resulting in the lumping of entities previously considered to be separate and the splitting of other entities previously considered the same. At the same time, the phenotypic limits of some XLID entities have been established with some degree of objectivity.

Several XLID entities have been most instructive. Discovery that mutations in the *ATRX* gene (Xq21.1) cause Alpha-Thalassemia Intellectual Disability allowed testing of large number of males with hypotonic facies, intellectual disability, and other features (Gibbons et al. 1995a, 1995b; Villard and Fontes 2002). Five named XLID syndromes – Carpenter–Waziri, Holmes–Gang, Chudley–Lowry and XLID–Arch Fingerprints–Hypotonia – have been found to be allelic variants of Alpha-Thalassemia Intellectual Disability as have certain families with spastic paraplegia and nonsyndromal XLID (Abidi et al. 1999, Lossi et al. 1999, Stevenson et al. 2000, Guerrini et al. 2000, Yntema et al. 2002, Abidi et al. 2005). One family clinically diagnosed as Juberg–Marsidi syndrome was found to have an *ATRX* mutation (Villard et al. 1996). This is now known to be based on misdiagnosis of Juberg–Marsidi syndrome since the original family with this syndrome has a mutation in *HUWE1* at Xp11.22 (Friez et al. 2011). One family clinically diagnosed as Smith–Fineman–Myers syndrome was also found to have an *ATRX* mutation, although the gene has not been analyzed in the original family (Villard et al. 2000). A clinically similar condition, Coffin–Lowry syndrome, was found to be separate from Alpha-Thalassemia Intellectual Disability and due to mutations in the serine–threonine kinase gene, *RPS6KA3* (*RSK2*) located at Xp22.13 (Trivier et al. 1996).

Kalscheuer et al. (2003) found mutations in *PQBP1* (Xp11.23) in two named XLID syndromes – Sutherland–Haan syndrome and Hamel Cerebro-Palato-Cardiac syndrome – and in MRX55 and two other families with microcephaly and other findings. Lenski et al. (2004), Stevenson et al. (2005), and Lubs et al. (2006) added Renpenning, Porteous, and Golabi-Ito-Hall syndromes to the list of XLID syndromes caused by mutations in *PQBP1*. As with the *ATRX* phenotypes, a wide variety of phenotypic expressions result from different mutations in *PQBP1* and we remain challenged to better understand

the molecular and developmental mechanisms leading to these differences (Germanaud et al. 2011, Sheen et al. 2010, Musante et al. 2010).

ARX (Xp22.11) was also found to be an important XLID gene encompassing multiple phenotypes. Mutations, most commonly a 24 bp expansion of a polyalanine tract, were found in a number of nonsyndromal families (MRX29, 32, 33, 36, 38, 43, 54, and 76), an X-linked dystonia (Partington syndrome), X-linked infantile spasms (West syndrome), X-linked lissencephaly with abnormal genitalia, hydranencephaly and abnormal genitalia, and Proud syndrome (Strømme et al. 2002a, 2002b; Bienvenu et al. 2002, Frints et al. 2002, Kitamura et al. 2002, Uyanik et al. 2003, Kato et al. 2004, Stepp et al. 2005).

Perhaps the most prominent example of syndrome splitting is FG syndrome. This syndrome, initially described in 1974 by Opitz and Kaveggia, is manifest by macrocephaly (or "relative macrocephaly"), downslanting palpebral fissures, imperforate anus or severe constipation, broad and flat thumbs and great toes, hypotonia, and intellectual disability. In the ensuing years, the manifestations attributed to FG syndrome have become protean, but none was pathognomonic or required for the diagnosis (Opitz et al. 1988, Romano et al. 1994, Ozonoff et al. 2000, Battaglia et al. 2006). Clinical heterogeneity was thus introduced and as a result different families were found to have different localizations on the X chromosome (Briault et al. 1997, 2000; Piluso et al. 2003, Dessay et al. 2002, Jehee et al. 2005, Tarpey et al. 2007, Unger et al. 2007).

In 2007, Risheg et al. found a recurring mutation, pR961W, in *MED12* (Xq13.1) in six families with the FG phenotype, including the original family reported by Opitz and Kaveggia. In addition to the above noted manifestations, two other findings, small ears and friendly behavior, were consistently noted.

Although most patients that have carried the FG diagnosis have one or more findings that overlap with those in FG syndrome, they do not have *MED12* mutations (Lyons et al. 2009, Clark et al. 2009). Some have been found to have other X-linked gene mutations (*FMR1*, *FLNA*, *ATRX*, *CASK*, *MECP2*) and others have had duplications or deletions of the autosomes (Lyons et al. 2009, Clark et al. 2009). So great is the currently existing heterogeneity within FG syndrome, that the vast majority of individuals so designated should best be considered to have intellectual disability of undetermined cause. The designation of multiple loci on the X chromosome for FG syndrome appears to be ill conceived (Opitz et al. 2008) and illustrates the hazards involved in nosology without a laboratory basis.

In a number of instances, certain mutations of genes have been associated with nonsyndromal XLID while other mutations of the same genes have caused syndromal XLID. Seventeen genes that may cause either type of XLID, depending on the mutation, have been identified (www.ggc.org/xlmr.htm, Figure 2). In some cases (e.g., those with *OPHN1* and *ARX* mutations) reexamination has found syndromal manifestations in families previously considered to have nonsyndromal XLID (Turner et al. 2002, Frints et al. 2002, Bergmann et al. 2003, Philip et al. 2003).

The frequency with which the process of lumping and splitting in this limited field of investigation has occurred has been extremely instructive to both clinical and molecular investigators. The underlying mechanisms or pathways by which mutations in different genes result in similar phenotypes and different mutations in a single gene result in disparate phenotypes, however, remain to be fully elucidated.

An exponential increase in the understanding of molecular pathways and neuronal complexes involved in brain function has occurred in the past decade. Many of the genes and their protein products involved in the critical processes of proper brain development and function – neurogenesis, neuronal migration, and synaptic connectivity – have been identified. It has become obvious that the "brain genes" may play multiple roles in these areas of central nervous system development at different critical developmental periods. Neurogenesis is likely affected by many X-linked genes given the finding of microcephaly in over 40 of the syndromes described in this text. Neuronal migration abnormalities are a common pathogenic finding on cranial imaging studies in individuals with mutations of *ARX*, *DCX*, and *FLNA*. Synaptic connectivity has emerged as the single most important functional deficit in individuals with ID and the synapse is the site of expression for a majority of the associated X-linked genes. Gene products are involved in pre- and post-synaptic processes of synaptic vesicles (*SYN1*, *SYP),* cellular adhesion (*L1CAM*, *NLGN3*, *NLGN4*, *PCDH19),* neurotransmitter release and receptor function (*GRIA3*, *IL1RAPL1*), neurite outgrowth and dendritic spine maturation (*FMR1*, *PAK3*, *OPHN1*), and cytoskeletal homeostasis (*CASK*, *FLNA*). Additionally, several X-linked genes function as transporters: *ATP7A*, *MED12*, *SLC16A2* (*MCT8*) and *SLC6A8*, and transcription regulation and chromatin remodeling: *ARX*, *MECP2*, *KDM5C*, *RPS6KA3*, *BRWD3* and *ATRX*. Rho GTPase genes – *ARHGEF6*, *ARHGEF9*, *OPHN1*, *GDI1*, *FGD1* and *PAK3* – mediate organization of the cytoskeleton, cell shape, and motility. The RAS-MAPK transcription-signaling cascade includes proteins encoded by *ARX*, *PHF6*, *ZNF41*, *PAK3*, and *RPS6KA3*. Some genes are involved in basic cellular processes, including RNA splicing (*PQBP1*), translation (*FTSJ1*), energy metabolism *(SLC6A8),* endocytosis (*DLG3, AP1S2*), ubiquitination (*CUL4B*, *UBE2A*) and nonsense mediated decay *(UPF3B)*. Elucidation of the molecular etiology of Fragile X syndrome has allowed greater understanding of the interplay and balance necessary between both excitatory glutaminergic and inhibitory GABAergic neurons, and provided insight to possible treatments targeted at restoring this balance, an approach that may also be applicable to other types of ID and autism.

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Numerous authors and publishers have provided figures to illustrate the XLID syndromes. Individual credits are given in the figure legends. Literature searches, citation verification, and other library resources have been provided by Rachel Collins. Karen Buchanan and Patti Broome have organized the materials used to produce this monograph and have provided invaluable assistance and advice.

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AARSKOG SYNDROME

(AARSKOG-SCOTT SYNDROME, FACIOGENITAL DYSPLASIA, FACIODIGITOGENITAL SYNDROME)

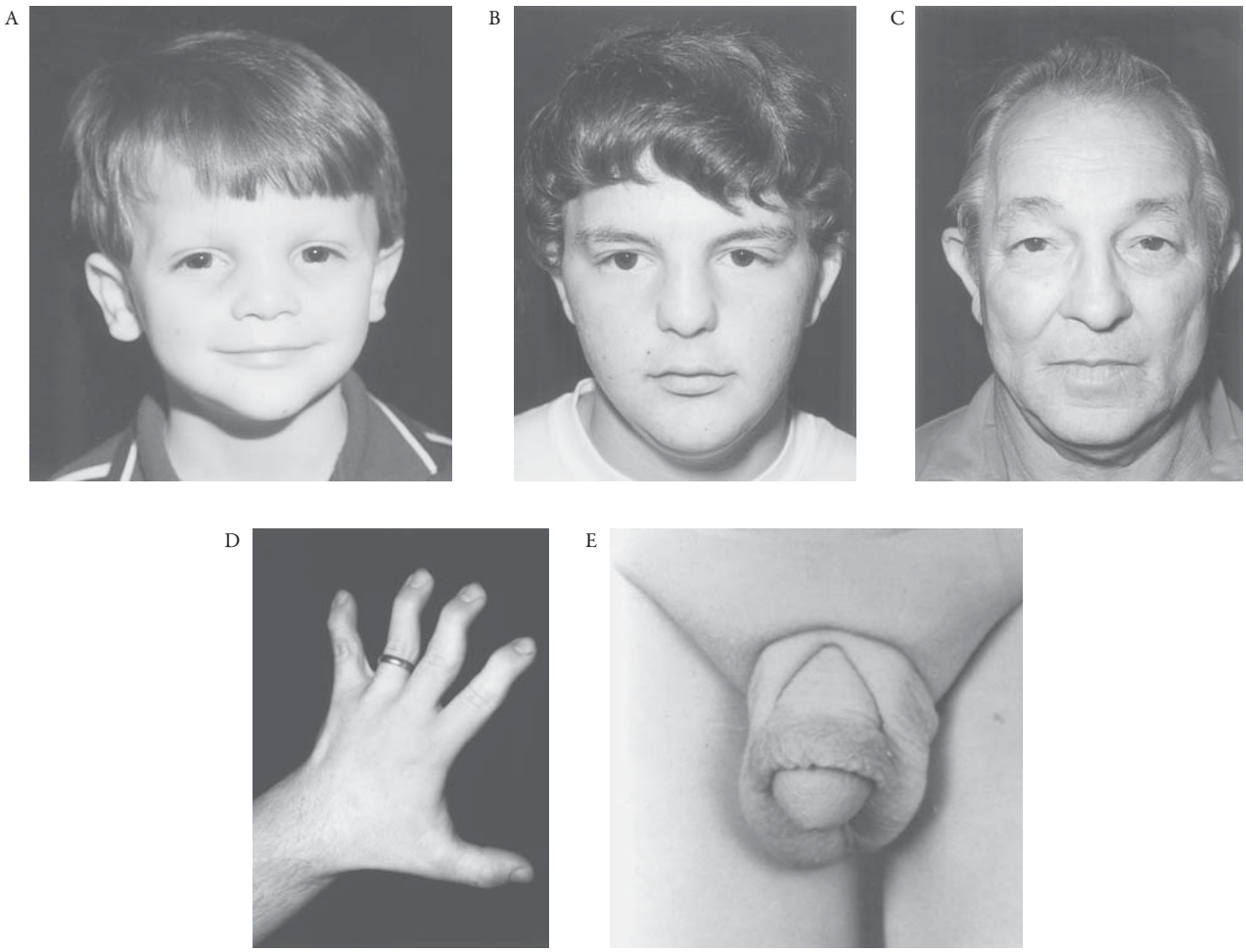
OMIM 305400

Xp11.22

FGD1

Definition. XLID with short stature, hypertelorism, downslanting palpebral fissures, joint hyperextensibility, and shawl scrotum. The gene (*FGD1*), a guanine nucleotide exchange factor, exerts its influence, at least in part, by activating Rho GTPase. More than 100 mutations, the majority of which lead to truncated proteins, have been identified.

Somatic Features. Prominent forehead, widow's peak, hypertelorism, downslanting palpebral fissures, ptosis, short nose with anteverted nares, cupped ears, wide upper lip, indistinct philtral pillars, and small chin comprise the facial phenotype. In adults, the face elongates and the prominent forehead and hypertelorism may not be apparent. When extended, the fingers are held in flexion at the MP joints, hyperextension at the PIP joints, and flexion at the DIP joints, presumably because of shortening of the flexor tendons. Other musculoskeletal findings include brachydactyly, horizontal palmar crease, varus foot, and generalized joint hyperextensibility. The scrotum tends to surround the penis,



Aarskog Syndrome. Four-year-old with hypertelorism, downslanting palpebral fissures, and prominent forehead **(A)**; 17-year-old with prominent forehead, ptosis, and cupped ears **(B)**; 60-year-old with balding and cupped ears but less apparent widening of midface **(C)**; characteristic posturing of extended fingers **(D)**; shawl scrotum **(E)**.