# SYNDROMIC CLASSIFICATION OF HEREDITARY LYMPHEDEMA

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"Vertebrate development is constrained into only a very few final or common developmental pathways; therefore, no developmental anomaly seen in humans is unique to ('pathognomonic of') one syndrome."

JM Opitz (1)

*ABSTRACT*

*Since the late 1800's, the familial occurrence of peripheral lymphedema has been well-documented in Milroy and Meige syndromes. However, the presence of lymphedema in many other hereditary dysmorphic syndromes has not been fully appreciated. In order to establish more standardized and detailed clinical phenotypic criteria as the basis for rational classification and for greater precision in screening and genetic linkage studies, we conducted a comprehensive literature search and review of OMIM-identified and non-identified hereditary syndromes in which lymphedema was reported as a feature. Modes of inheritance, associated clinical features and images, and specific organ involvement were inventoried and suggested pathophysiologic mechanisms noted. The findings support the recommendation that when peripheral lymphedema of undetermined etiology is found, further careful, comprehensive clinical, including detailed dysmorphic, evaluation along with lymphatic imaging with subsequent syndromic classification is warranted. This information can provide clues to underlying pathogenesis and form the basis for genetic counseling and prognostication as well as offer guidance to the clinical investigator translating research at the molecular level into new approaches for evaluation and therapy.*

Whereas the familial occurrence of peripheral lymphedema has been recognized for more than 150 years, it was not until 1998 that candidate loci or genes were described for congenital onset lymphedema or Milroy disease (2-4). Meige syndrome, a second common hereditary lymphedema syndrome with pubertal onset also has unknown genetic loci except for the specific syndrome of Lymphedema-distichiasis (5). With recent advances in understanding of the growth and development of the lymphatic vasculature ("lymphangiogenesis") (reviewed in 6-8), following close on the heels of exploding knowledge about analogous processes in the blood vasculature ("hemangiogenesis", imprecisely termed "angiogenesis"), great interest has surrounded the isolation, discovery, and/or reporting of genes and proteins underlying hereditary lymphedemas in man and parallel studies of genetically engineered lymphedema syndromes in non-

human species. Accordingly, a more thorough description of the spectrum of clinical phenotypes including specific lymphatic abnormalities seen in the familial lymphedemas, beyond what we have reviewed in prior publications (9,10) is timely and indeed past due.

Several key members of the vascular endothelial growth factor (VEGF) (11) and angiopoeitin (12) families of vascular growth factors and their related tyrosine-kinase endothelial receptors appear to selectively influence lymphatic growth and remodeling. Other growth factors, receptors, cell surface proteins and transcriptional elements have also been implicated in lymphatic development and the regulation of boundaries between different segments of the vasculature (e.g., ephrins). Some of these have been useful as distinctive markers for lymphatic vessels on tissue section (e.g. Prox1, LYVE-1, and podoplanin) (8).

Mutations in three different genes have been implicated in the origin of three distinct familial lymphedema-angiodysplasia (LE-AD) syndromes. Some families (approximately 5%) (11) with autosomal dominant Milroy disease, as mentioned earlier, show mutations for *VEGFR3* (chromosome 5q35.3), the endothelial receptor for VEGF-C and D, but most others do not (3,13,14). In autosomal dominant Lymphedema-distichiasis (double row of eyelashes) with onset of peripheral lymphedema at puberty, mutations in the *FOXC2* forkhead transcription factor (chromosome 16q24.3) (5), which is involved in a number of developmental processes, have been consistently documented in 33 families (5,15-17). In addition, mutations in the *SOX18* transcription factor located on chromosome 20q13, have been reported in association with both an autosomal recessive and autosomal dominant (or gonadal mosiacism) forms of Hypotrichosis-lymphedema-telangiectasia (18). Three additional members of the *SOX* family of transcription factors are associated with human disease. Mutations in the *SRY*

gene (Yp11.3) are associated with gonadal dysgenesis and sex reversal; mutations in *SOX9* (17q24.3-q25.1) are associated with camplomelic dysplasia and autosomal sex reversal; and mutations in *SOX10* (22q13) cause Waardenburg-Hirschsprung syndrome (18). This finding may bring particular interest to prior and new reports of lymphedema and other phenotypic Turner syndrome-like features in Gonadal Dysgenesis, XY females, and also a hereditary form of Campomelia segregating with congenital lymphedema inherited in an autosomal recessive type pattern.

Clinical syndromes involving altered lymphvascular phenotypes are typically described by their inheritance patterns, age of onset, and body sites affected. The phenotype not only reflects the specific mutated genes and proteins but also the epigenetic including environmental influences and interactions between the lymphatic and other body systems. Even within a family or syndrome complex, there is wide clinical variability suggestive of reduced penetrance, genetic heterogeneity, modifier genes, or other unrecognized molecular-based phenomena.

Most LE-AD syndromes have congenital onset lymphedema of the lower limbs, but others are associated with more extensive edema, chylous ascites, pleural effusions or specific related lymphatic growth disturbances such as cystic hygromas, lymphangiomas, or fetal hydrops, and even fetal demise. Accordingly, the true incidence of primary lymphangiodysplasias is hard to quantify. In disorders with multiple congenital anomalies consistently shared within a syndrome and/or family, a common defect(s) early in development is likely. Later onset or pubertal manifestations suggest incomplete penetrance with specific gene polymorphisms, different molecular deficits within the same metabolic or developmental pathway, or other poorly understood complicating variables including regulatory genes, epigenetic influences, chemical mediators, and environmental factors.

## TABLE 1
### List of Lymphedema-Associated Syndromes

**OMIM Listed and reference number**

| | | | |
|---|---|---|---|
| LE-Distichiasis | 153400 | Prolidase Deficiency (PEPD) | 170100 |
| Cholestasis-LE (Aagenaes) (CLS) | 214900 | Intestinal Lymphangiectasia (IL) | 152800 |
| LE-Hypoparathyroidism (LE-HypoPTH) | 247410 | NAGA Deficiency (NAGA) | 104170 |
| LE, Microcephaly, Chorioretinopathy | | Aplasia Cutis Congenita with IL (ACC-IL) | 207731 |
| (LE-M-R) | 152950 | Mullerian Derivatives- LA-Polydactyly | |
| LE, Congenital Recessive (Mucke) | 247440 | (PMD-IL) (Urioste Syndrome) | 235255 |
| LE-Ptosis | 153000 | Pulmonary Cystic Lymphangiectasia (PCL) | 265300 |
| Hennekam Lymphangiectasia | 235510 | CDG, subtype (Jaeken) | 602579 |
| LE, Cerebral Arteriovenous Anomaly | | Nevo Syndrome | 601451 |
| (LE-CVA) | 152900 | PEHO Syndrome | 260565 |
| Yellow Nail Syndrome (YNS) | 153300 | Hypotrichosis-LE-Telangiectasia (HTLS) | 607823 |
| LE, ASD, and Facial Changes (LE-ASD) | 601927 | Tuberous Sclerosis, variant | 191100 |
| OL-EDA-ID | 300301 | | |
| Noonan Syndrome | 163950 | | |
| German Syndrome | 231080 | **Non-OMIM Listed** | |
| Campomelia, Cumming type | 211890 | | |
| Fabry disease, variant | 301500 | Posterior Choanal atresia-LE (Sheikh) Syndrome | |
| Aarskog Syndrome, variant | 100050 | (PCA-LE) | |
| Lissencephaly-Cerebellar hypoplasia-LE | | LE-leukaemia-deafness (Emberger) Syndrome | |
| (LE-CHL) | 257320 | LE- Cleft Palate (Figueroa) Syndrome (CP-LE) | |
| Gonadal Dysgenesis (GD,XY) | 306100 | Microcephaly-Cutis Verticis Gyrata-LE (M-CVG-LE) | |
| Hydrops Fetalis, Idiopathic (Njolstadt) (IHF) | 236750 | Mandibulofacial Dysostosis-lymphedema Syndrome | |
| Chylous Ascites, Autosomal Recessive | 208300 | (MD-LE) | |

LE= lymphedema; LA- lymphangiectasia; IL= intestinal lymphangiectasia; ASD= atrial septal defect. OL-EDA-ID=Osteopetrosis, lymphedema, ectodermal dysplasia, anhidrotic, with immunodeficiency, NAGA= N-Acetyl-Alpha-D-Galactosaminidase, CDG=Congenital disorder of glycosylation, PEHO= Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy.

Our task was to perform a comprehensive review of the reported hereditary syndromes associated with lymphedema as an external manifestation of an underlying "lymphangiodysplasia," (abnormal lymphatic growth) (lymphedema-angiodysplasia syndromes or LE-AD) with an eye to elucidating the following questions: What other organ systems are affected and in what patterns in these LE-AD syndromes? Could there be a common pathway, embryological defect, or cause/effect explanation for these conditions? Could the information accrued help identify candidate loci for these or other multiple congenital anomalies (MCA) that share some of these features? What are important factors for the future evaluation and classification of newly reported cases?

## MATERIALS AND METHODS

Because the syndromes had not been gathered together under a single rubric, a literature review was conducted for symptoms and signs of hereditary LE-AD syndromes listed in OMIM (the Online Mendelian Inheritance in Man database (19). Multisystem manifestations were listed and their frequency determined (syndromes exhibiting particular manifestations divided by the total number of distinct LE-AD syndromes. Where published, images of the abnormalities in specific syndromes were reproduced.

Within the multitude of syndromes and families reviewed, we sought to document the lymphvascular phenotype (i.e., hypoplastic,

## TABLE 2
### Autosomal Dominant Lymphedema Syndromes

| System Involvement | YNS | Noonan | Emberger | LE-Ptosis | LE-Distichiasis | IL | LE-CVA | LE-M-CR | CP-LE |
|---|---|---|---|---|---|---|---|---|---|
| Growth/Bone | | + | | | + | | | + | |
| Mental Retardation | | | | | | | + | + | |
| CNS | | + | | | | | | + | |
| Cranial | | + | | | | | | + | |
| Ocular | + | + | | + | + | | | + | |
| Special Senses | | | + | | | | | | |
| Dysmorphic Faces | | + | | | + | | | + | + |
| Skin/Nails | + | | | + | | | | + | |
| Thoracic/Vertebral | + | + | | | | | | | |
| Limb Defects | | | | | | | | | |
| Joints | | | | | | | | | |
| Pulmonary | + | + | | | | + | + | | |
| Cardiac | | + | | | + | | | + | |
| Gastrointestional | + | + | | | | + | | | |
| Genitourinary | + | + | | | + | | | + | |
| Immune Dysfunction | | + | | | | + | | | |
| Hematologic | | + | | + | | + | | | |
| Malignancy | + | | + | + | + | | | | |
| F:M > 2:1 | | + | | | | | | | |
| M:F > 2:1 | | | | + | + | | + | | |

aplastic, hyperplastic) including areas of involvement such as specific limbs or limb portions and visceral lymphatic involvement as well as abnormalities of other organ systems. The sex ratio, presence of consanguinity, and other potential environmental factors were catalogued to specify better the distinct features unique to each syndrome.

Based on this literature review, 36 total syndromes (other than Milroy and Meige) were identified that had primary lymphedema as a reported clinical feature at least in some patients *(Table 1)*. Most were retrieved through an OMIM search (keyword "lymphedema" or "lymphangiectasia") (19) or from an earlier summary of lymphatic maldevelopment syndromes initially presented by Hennekam at the National Lymphedema Network Biennial Conference in Orlando, Florida in September 2000 and subsequently published (20). Of the OMIM-listed syndromes, some were excluded from the review for the following range of reasons; variant forms of another syndrome already included, phenotypic ambiguity, primary lymphedema without a suggested heritable pattern, syndromes suggestively arising from

**TABLE 3**
**Autosomal Recessive Lymphedema Syndromes**

| System Involvement | Nevo | PEHO | CDG | German | LE-CHL | Hennekam | M-CVG-LE | Campomelia | PMD-IL | LE-ASD | ACC-IL | IHF | PCA-LE | Mucke | NAGA | PEPD | Chylous Ascites | CLS-Aageneas | PCL | HLTS | Tuberous Sclerosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Growth/Bone | | + | + | + | + | + | | + | + | | | + | | | | | + | + | | | |
| Mental Retardation | | + | + | + | + | + | | | | | | | | + | + | + | | | | | + |
| CNS | + | + | + | + | + | + | + | | | | | | | | | | | | | | + |
| Cranial | + | + | + | + | | + | + | + | + | + | + | | | | | | | | | | |
| Ocular | + | + | + | + | + | + | + | | + | + | | + | + | + | + | + | + | + | | + | |
| Special Senses | | + | | | | + | | + | + | | | | | | | | | | | | |
| Dysmorphic Faces | + | + | + | + | | + | | + | + | + | | + | + | + | + | | | | | | |
| Skin/Nails | + | + | + | + | | + | | + | + | + | + | | | | | | | | | + | + |
| Thoracic/Vertebral | + | + | + | + | | + | | + | | + | | + | + | | | | | | | | |
| Limb Defects | + | + | + | + | | + | + | + | | | + | | | | | | | | | | |
| Joints | + | + | + | + | | + | | + | | | | | | | | | | | | | |
| Pulmonary | | + | | + | | + | | + | | | | + | | | | | | | + | + | |
| Cardiac | | | + | | + | + | + | + | | + | | | + | + | + | | | | | | |
| Gastrointestinal | | | + | + | + | + | + | + | | | + | + | | + | | + | + | + | + | | |
| Genitourinary | + | + | + | + | | + | | + | | + | | + | | + | | + | + | | | + | |
| Immune Dysfunction | + | | + | | | + | + | + | | | + | | | | | + | | | | | |
| Hematologic | | | + | | | | | | | | + | + | | + | | | | | + | | |
| Malignancy | | | | | | | | | | | | | | | | | | + | | | |
| F:M > 2:1 | | + | | | | | + | + | | | | + | | | | | + | | | | + |
| M:F > 2:1 | + | | + | | + | | | | + | + | + | | | + | | | | | | | |

intrauterine edema, or separate entries for associated genetic loci or gene products. For several syndromes, the number of patients were few and sometimes within one family. Some were isolated, atypical case reports of another previously described syndrome. Many features were described for most affected patients; however, there were wide variations in available clinical information, the work-up performed on each patient, and the inclusion of family members in the medical evaluation. Inheritance patterns could not always be confirmed in syndromes with small numbers of affected or available familial data and occasionally varied within a syndrome. Other syndromes included were

listed by Hennekam (20), without an associated OMIM entry, bringing the grand total to 36. References were typically original case reports, recent and/or large reviews, or familial studies appearing in journals of clinical genetics or pediatrics *(see References)*.

*RESULTS AND COMMENTS*

*Tables 2-4* summarize data on reported organ/system involvement in autosomal dominant (*Table 2*, compilation based on references 21-38), autosomal recessive (*Table 3*, compilation based on references 39-65), and X-linked (*Table 4*, compilation based on references 66-74) LE-AD syndromes. Single

| | TABLE 4 — X-Linked Lymphedema Syndromes | | | | | |
|---|---|---|---|---|---|---|
| System Involvement / Syndrome | OL-EDA-ID | LE-HypoPTH* | Aarskog* | GD-XY | Fabry's* | MD-LE* |
| Growth/Bone | + | + | + | + | | + |
| Mental Retardation | | | | | | |
| CNS | | | | | | + |
| Cranial | | | | | | + |
| Ocular | | + | + | | | + |
| Special Senses | | | | | + | + |
| Dysmorphic Faces | + | + | + | | | + |
| Skin/Nails | | + | | | | + |
| Thoracic/Vertebral | + | | + | + | | + |
| Limb Defects | | + | + | | | + |
| Joints | | | | | | + |
| Pulmonary | | + | | | | + |
| Cardiac | | + | | | | + |
| Gastrointestional | + | | | | | + |
| Genitourinary | | + | + | | + | + |
| Immune Dysfunction | + | + | | | | + |
| Hematologic | + | + | | | + | + |
| Malignancy | | | | + | | |
| F:M > 2:1 | | | | + | | |
| M:F > 2:1 | + | + | + | | + | + |

asterisks indicate syndromes where alternative inheritance patterns were proposed. *Figs. 1-10* illustrate other characteristic phenotypic features described by organ system in hereditary LE-AD syndromes. *Fig. 11* summarizes the frequency of autosomal dominant, autosomal recessive and X-linked inheritance patterns in these hereditary syndromes subdivided by age of onset. *Fig. 12* summarizes, in declining order, the overall frequency of specific organ/system involvement reported for the 36 syndromes. In the text, numbers in italics in brackets represent the number of syndromes of the 36 which exhibited the designated phenotypic feature.

## Central Nervous System Anomalies (Fig.1A-J, References 60,75-81; Tables 2-4)

Of the 36 LE-AD syndromes reviewed, 11 (31%) had Central Nervous System (CNS) or cranial abnormalities. The most common were hypotonicity *[n=7] (Fig. 1A)*, atrophy of cerebrum or cerebellum *[6] (Fig. 1B)*, seizures *[6]*, and spasticity *[3]*. In 7 of the 11, the CNS anomaly was the major clinically defining feature of the syndrome. In cerebellar-hypoplasia-lymphedema-lissencephally, two families demonstrating autosomal recessive inheritance had two different mutations in the gene *RELN* (encoding a protein "reelin") that maps to chromosome 7q22. This gene encodes a secreted protein that acts on migrating cortical neurons by binding to the low-density lipoprotein receptor (VLDLR), the apolipoprotein E receptor (ApoER2), alpha-3, beta-1 integrin, and protocadherins. This protein was originally thought to be expressed only in the brain; however, based on the abnormalities of congenital, intractable lymphedema and one patient with chylous ascites, there may be another role of *RELN* in serum homeostasis perhaps through interactions with low density lipoprotein (LDL) superfamily receptors outside the brain (82). The high frequency of hypotonia in these reports may be attributed to either neurological developmental delay or perhaps to congenital lymphedema. Opitz (1) and Lewin (80) proposed a hypotonia-hypokinesia sequence, i.e., limited fetal tone and movement as the basis for the persistence of congenital lymphedema. Rauch et al (83) described a novel clinically distinct 5q35.3 subtelometric deletion syndrome with prenatal lymphedema, developmental delay, hypotonia, short stature, congenital heart abnormalities, thorax abnormalities and a distinct facial gestalt. The gene for VEGFR3 is already known to lie in this region but warrants further evaluation when comparing the phenotypic features in this patient with others with microdeletions of this region, such as Sotos Syndrome, to delineate more
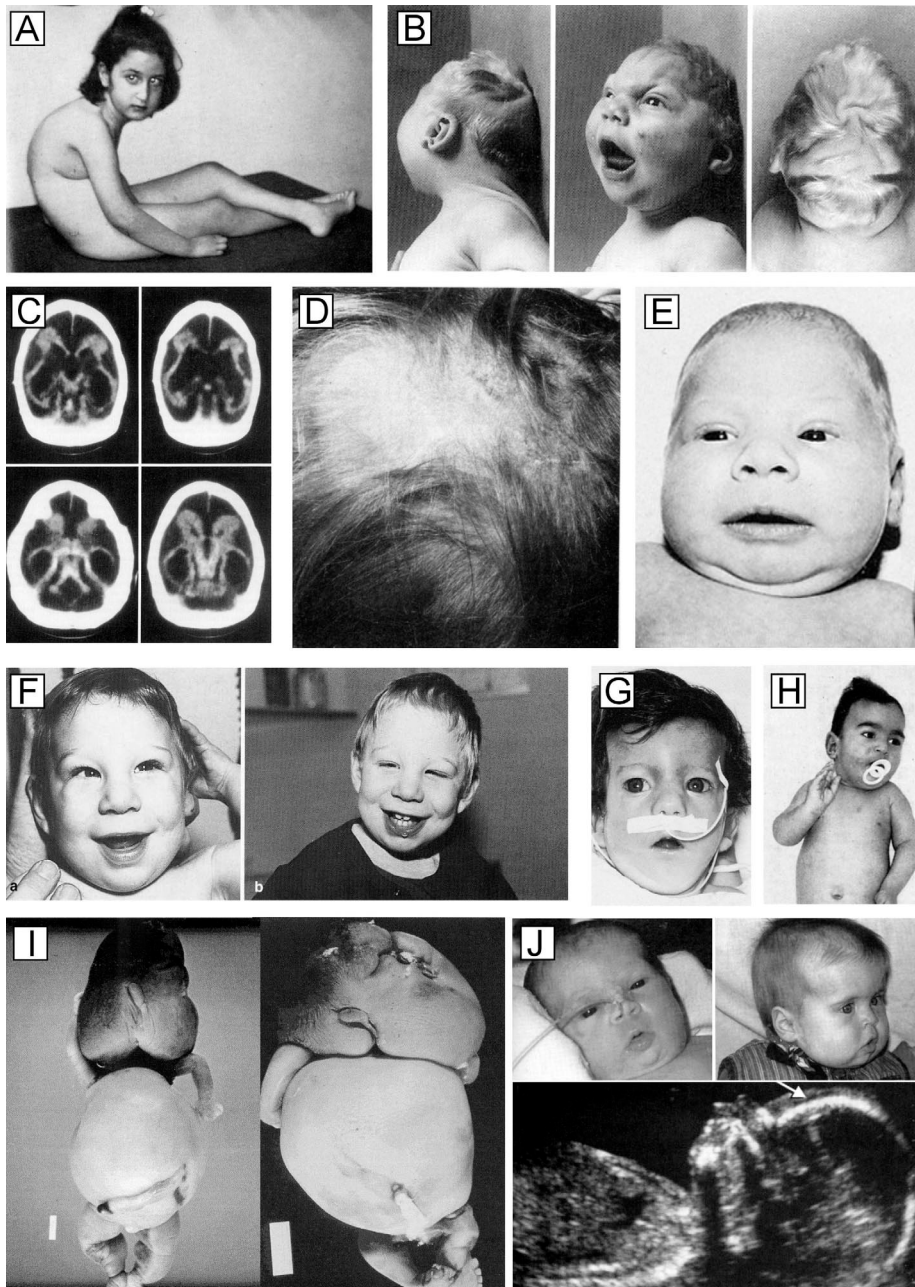
*Fig. 1. Central Nervous System and Skull Manifestations in Hereditary Lymphedema Syndromes. A. Hypotonia, dolicocephaly and kyphosis in Nevo syndrome. B. Cerebral hypoplasia and scalp defect in Cutis Vertica Gyrata. C. CT head in Cutis Verticis Gyrata-Lymphedema syndrome. D. Scalp defect in Aplasia Cutis Congenita-Intestinal Lymphangiectasia. E. Microcephaly in Microcephaly-chorioretinopathy dysplasia-lymphedema (LE-M-CR) syndrome. F. Microcephaly in LE-M-CR at 6 weeks and 15 months of age. G. Dolicocephaly in German syndrome. H. Dolicocephaly in Nevo syndrome. I. Cloverleaf skull deformity and short limbs in Campomelia, Cumming type fetuses. J. Progressive hydrocephaly including head ultrasound in Persistent mullerian derivatives with intestinal lymphangiectasia. Reproduced with permission of J. Med. Gen. [A,H (73)]; Euro. J. Ped. [B,C (76)]; Am. J. Dis. Child. [D (75)]; Am. J. Med. Gen. [E (76), G (78), I (60), J (81)]; Clin. Gen. [F (79)].*
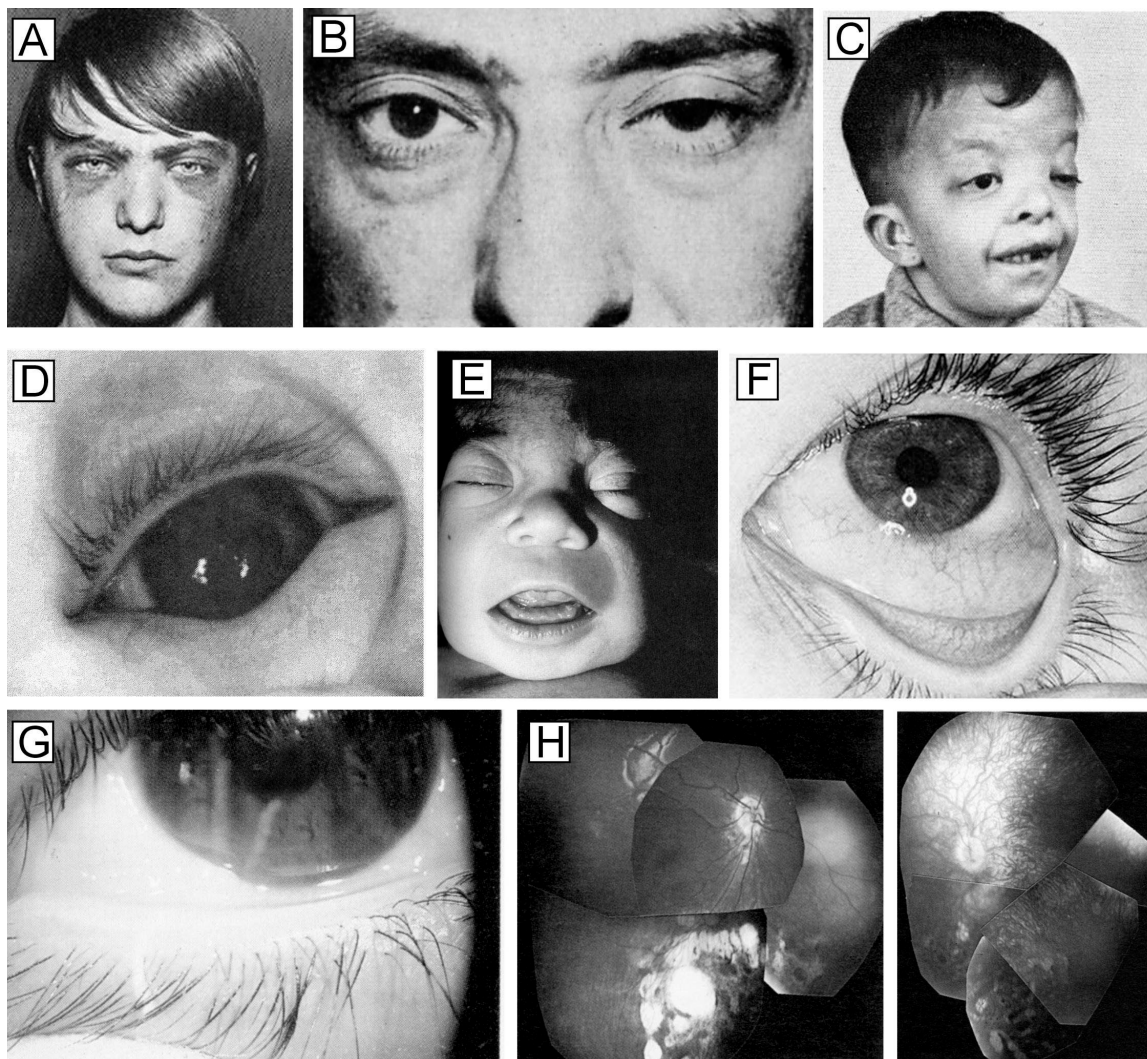
Fig. 2. Ocular Abnormalities in Hereditary Lymphedema Syndromes. A. Ptosis, conjunctival edema, and medial eyebrow flare in Lymphedema-hypoparathyroidism syndrome. B. Unilateral ptosis in Lymphedema-ptosis syndrome. C. Ptosis and hypertelorism in Noonan syndrome with intestinal lymphangiectasia. D. Ectropion uvae and E. Bilateral subepicanthal folds with facial edema in Persistent mullerian derivatives with intestinal lymphangiectasia. F. Conjunctival edema and chemosis in Mucke syndrome (autosomal recessive lymphedema). G. Distichiasis and chemosis in Lymphedema-distichiasis syndrome. H. Punched-out lesions in the retina of siblings with Chorioretinal dysplasia-lymphedema syndrome. Reproduced with permission from Am. J. Med. Gen. [A, (88), D (91), E 125)]; NY Med. J. [B (89)]; J. Ped. [C (90)]; Eur. J. Ped. [F (93)]; Arch. Ophthal. [G (94)]; Brit. J. Ophthal. [H (95)].

precisely the genotype-phenotype correlation (83).

Other sensory defects included deafness (reported in 5 syndromes), markedly impaired vision [6] (see *Ocular Anomalies*), and arrhinencephaly (absence of the nose or olfactory bulb) [1].

Structural cranial or brain anomalies occurred in 13 of 36 (38%) syndromes. Defects included abnormal skull shape [n=9], abnormal sutures or craniosynostosis [6], microcephaly [4], macrocephaly [3], and scalp defects [2] (Fig. 1B-D). These anomalies were a major feature in 3 of the 14
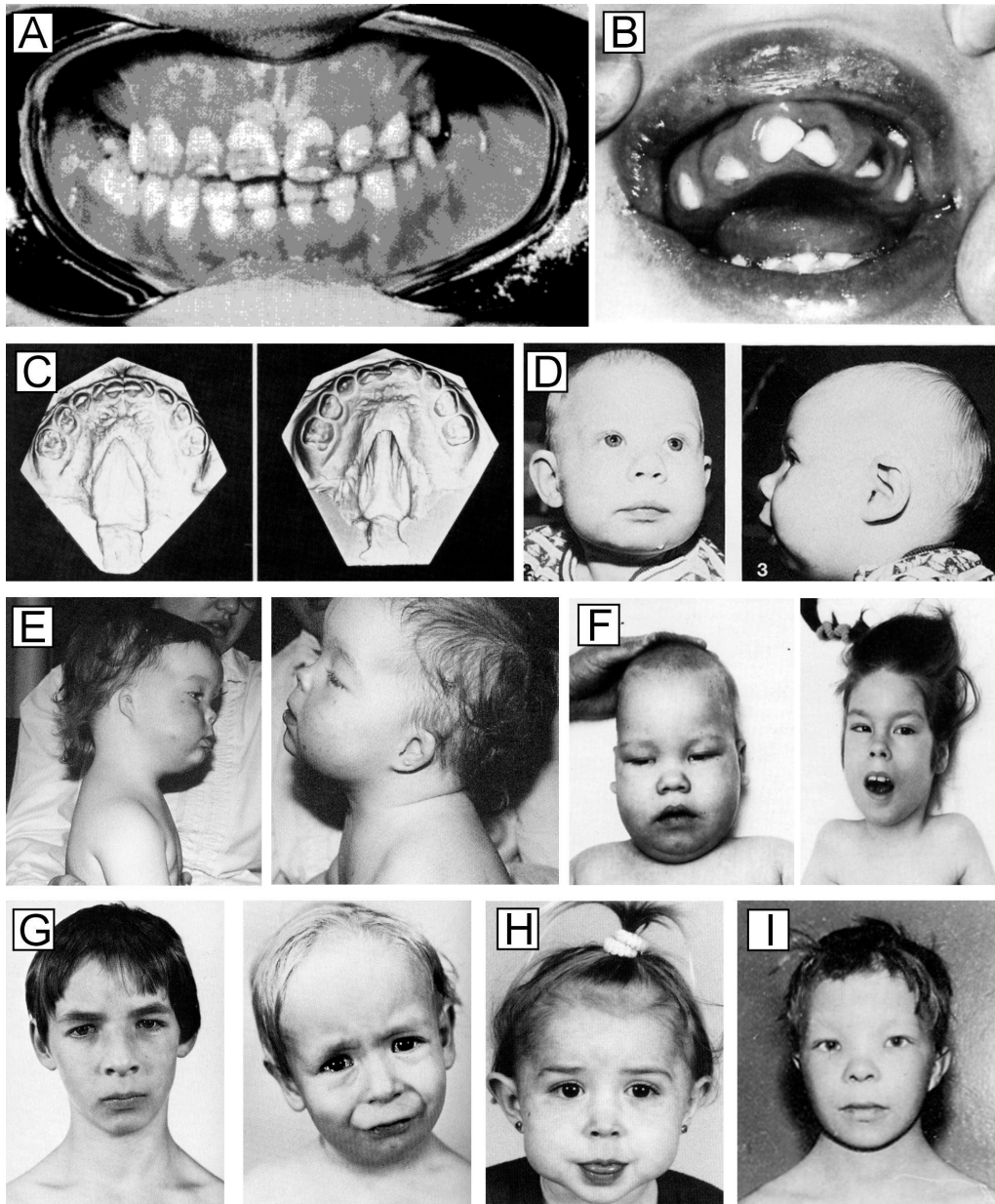
Fig. 3. Dysmorphic Facial Features in Hereditary Lymphedema Syndromes. A. Enamel defect and discolored teeth in Aagenaes syndrome. B. Gingival hypertrophy in PEHO syndrome. C. Cleft palate in Figueroa syndrome. D. Abnormal helices in Microcephaly-Chrioretinal Dysplasia-Lymphedema syndrome. E. Bilateral microtia with hearing loss in Mandibulofacial Dysotosis-Lymphedema syndrome. F. Dolicocephaly with narrow forehead, epicanthal folds, outward turning earlobes, and small chin in PEHO syndrome (see also Fig. 1G & 1H Dolicocephaly in German and Nevo syndromes). G. Thin upper lip, micrognathis, downslanting palpebral fissure, and euryblepharon in brothers with Mucke syndrome (autosomal recessive lymphedema). H. Thin upper lip and protruding ears in Njolstad syndrome (congenital pulmonary lymphangiectasia). I. Hypertelorism, upslanting palpebrl fissures, epicanthal folds, and flat nose in Aarskog syndrome. Reproduced with permission from Arch. Dis. Child. [A (105)]; J. Med. Gen. [B,F (106), I (110)]; Cleft Palate J. [C (107)]; Am. J. Med. Gen. [D (78), E (108), H (109)]; Europ. J. Pediat. [G (93)].
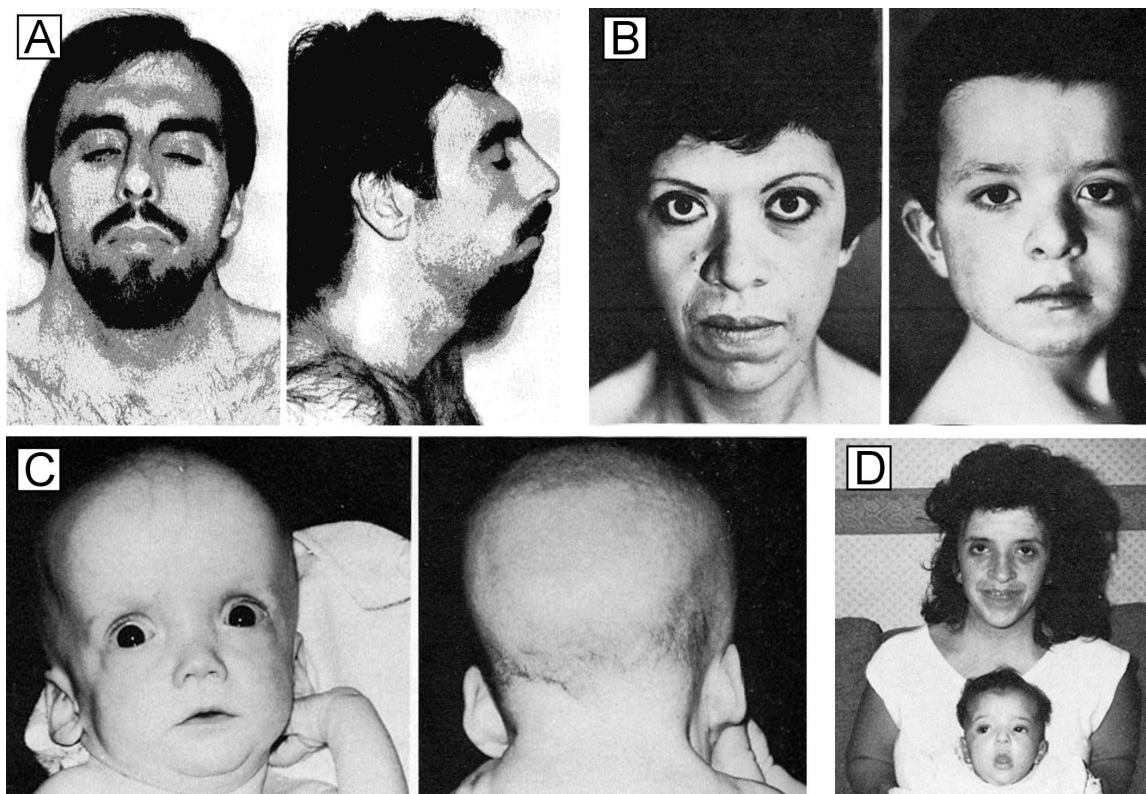
*Fig 4. A-D. Facial Features in familial Noonan syndrome associated with lymphedema. A. Micrognathia, webbed neck, and ptosis. B. Protruding ears and webbed neck in mother and daughter. C. Extreme ear protrusion and webbed neck. D. Protruding ears and webbed neck in mother and son. Reproduced with permission from Am. J. Med. [A (111)]; Am. J. Med. Genet. [B,C,D (112)].*

syndromes. Isolated microcephaly occurred mainly in an autosomal dominant pattern; however, in association with congenital lymphedema, it more commonly demonstrated predominantly autosomal recessive and/or X-linked inheritance (78,84) *(Fig. 1E,F)*. In some, mental retardation was observed whereas others had normal intelligence. In still other syndromes, autosomal recessive forms of microcephaly generally had more severe intellectual impairment, and in a few families there was linkage to chromosome 1q 25-32 (85). In syndromes with macrocephaly and lymphedema, 2 of 3 followed an autosomal recessive pattern and 1 of 3 an autosomal dominant pattern. Multiple hereditary syndromes with craniosynostosis have also been identified and several loci and candidate genes implicated. Of interest, one case of hereditary craniosynostosis, CRS2 (OMIM #04757) has been linked to mutations in *MSX2*, a homeobox gene which lies near the *VEGFR3* (5q35.3) gene implicated in several Milroy families. Two reported scalp defects have also been associated with other symptom complexes. Thus, Cutis Verticis Gyrata (CVG) is commonly associated with microcephaly and other cranial bony defects as part of a "fetal brain disruption sequence" with familial recurrence (76) *(Fig. 1B,C)*. Many patterns of inheritance of CVG have been described within other OMIM syndromes and studies by Musumeci et al. (86,87) suggested an association with chromosome fragile sites near Xq27.3 or 10q25 in patients with hereditary CVG. The
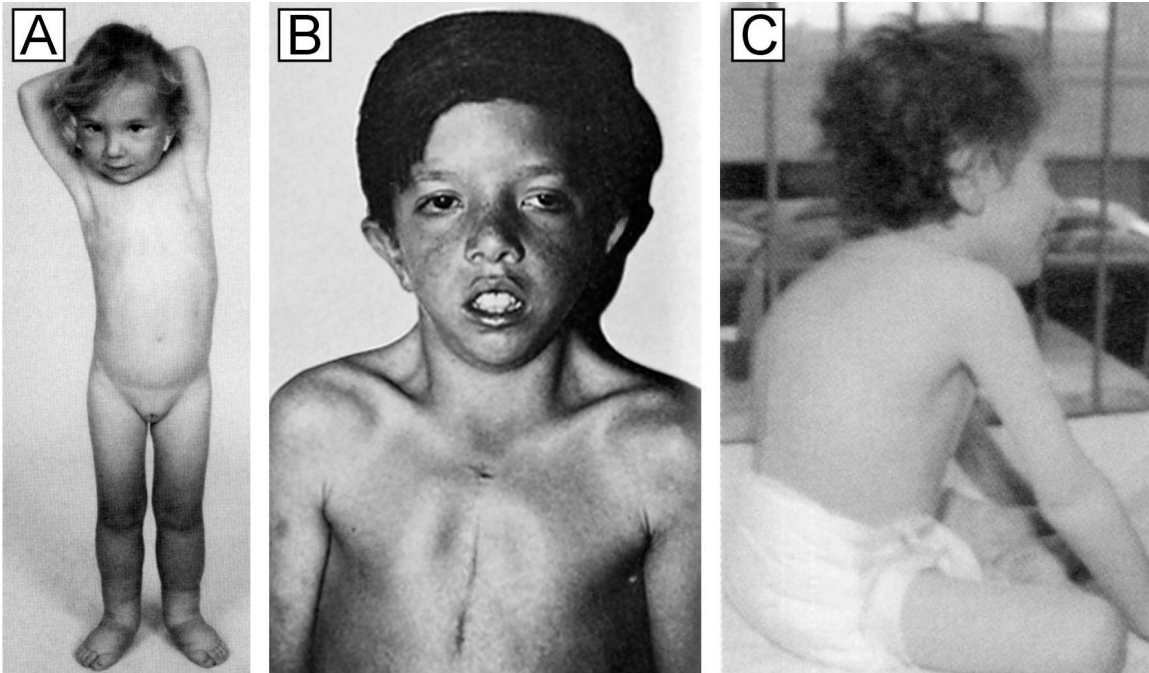
*Fig. 5. Skeletal Abnormalities in Hereditary Lymphedema Syndromes. A. Pectus excavatum in Njolstad syndrome (congenital pulmonary lymphangiectasia). B. Pectus carinatum superiorly and pectus excavatum inferiorly in Noonan syndrome. C. Kyphosis and knee flexures in CDG-Type I syndrome. D. Osteosclerosis of lower limbs in OL-EDA-ID syndrome. Reproduced with permission from Am. J. Med. Gen. [A (109), D (121)]; J. Med. Gen. [B (122), C (123)].*

other scalp defect, Aplasia Cutis Congenita (ACC) occurred in two brothers of a non-consanguineous marriage and was associated with intestinal lymphangiectasia. The investigator suggested an autosomal recessive defect in regulating the mesoectodermal development of the children and conducted an extensive review of other congenital malformations associated with ACC and their embryological tissue origin to support this hypothesis (77) *(Fig. 1D).*

Mental retardation and/or developmental delay was noted in 10 of the 36 LE-AD syndromes (29%) and in four of the 11, it was noted to be severe.

*Ocular Anomalies (Fig. 2A-H, References 88-95, Tables 2-4)*

Ocular abnormalities are common in LE-AD syndromes (24 of 36 or 67%). Six involved vision, i.e., absent visual response/optic atrophy *[n=4]*, severe myopia *[3]*, and amblyopia *[1]*. The others were usually structural defects: hypertelorism *[10]*, conjunctival vascular abnormalities or edema *[8]*, iris colobomata or unusual patterning or coloring *[7]*, ptosis *[5]*, slanted palpebral fissures *[5]*, epicanthal folds *[5]*, glaucoma *[3]*, or congenital cataracts *[2] (Fig. 2A-H).*

Hypertelorism is probably the consequence of arrest in development of the sphenoid bone making the greater wings smaller than the lesser wings and thereby fixing the orbits in a widely separated fetal position (19). This anomaly shows various inheritance patterns in many different syndromes. When associated with lymphedema, hypertelorism shows autosomal recessive inheritance in 7 of 10 syndromes
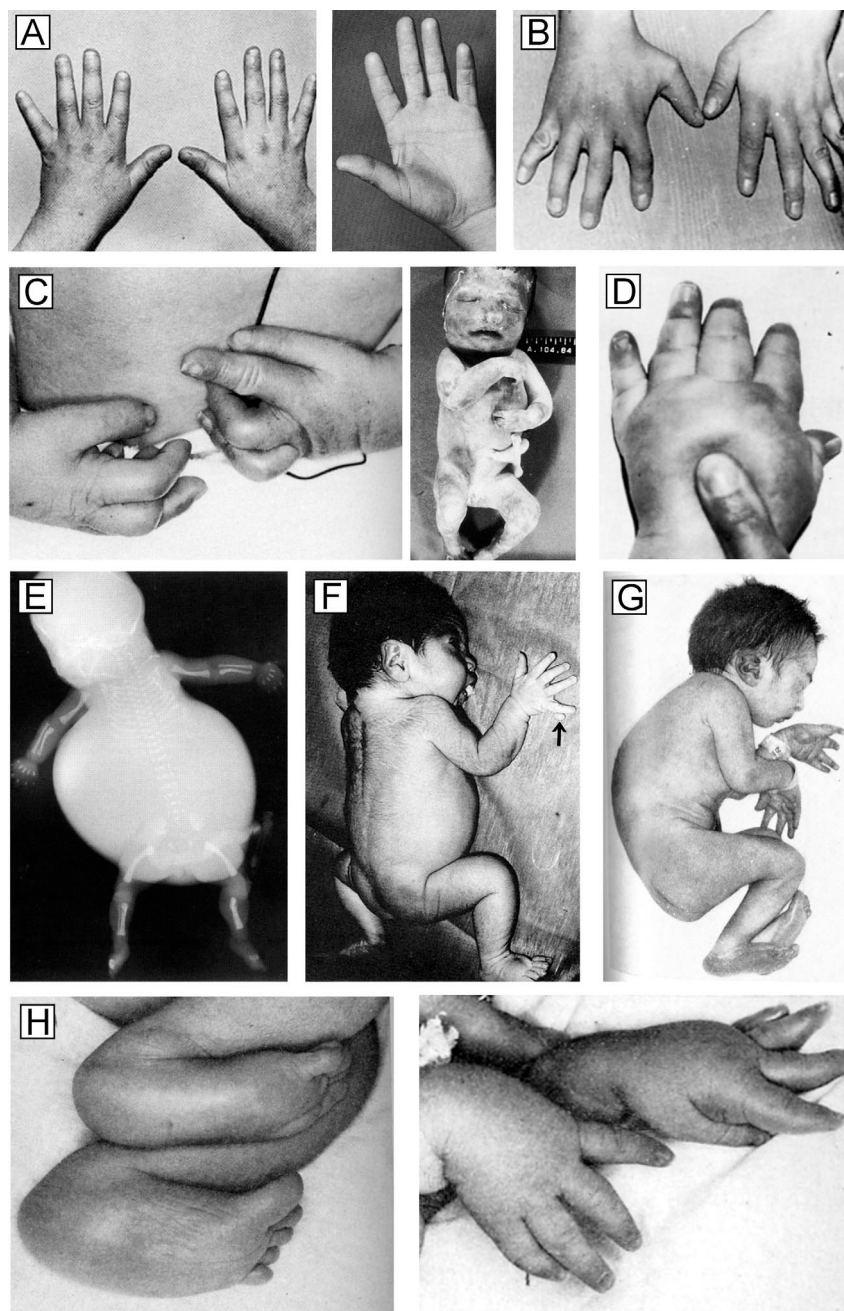
*Fig. 6. Limb Abnormalities in Hereditary Lymphedema Syndromes. A. Brachydactyly in sibs with Lymphedema-hypoparathyroidism. B. Campoclinodactyly in Aarskog syndrome. C. Campodactyly and flexion contractures in sibs with German syndrome. D. Dystrophic deep-set and distorted nails with volar edema in PEHO syndrome. E. Short limbs, small chest with flared ribs in Campomelia, Cumming type. F. Postaxial polydactyly and hirsutism in Persistent mullerian derivatives with intestinal lymphangiectasia. G. Spindle fingers, clinodactyly, wrist drop and dorsiflexion contractures and foot edema in Nevo syndrome. H. Dorsiflexion and contractures in Nevo syndrome (closeup of G). Reproduced with permission of Am. J. Med. Gen. [A (88), C (80), E (124), F (125)]; J. Med. Gen. [B (110), D (106), G,H (75)].*
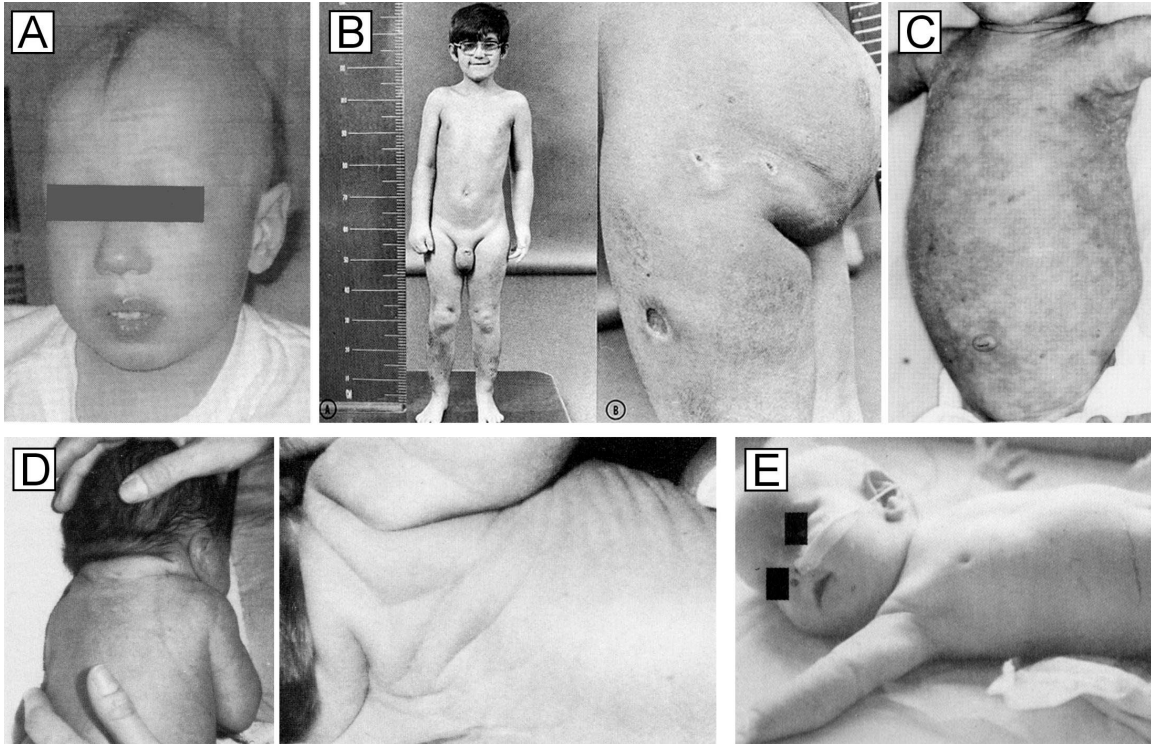
*Fig. 7. Skin and Integument Manifestations in Hereditary Lymphedema Syndrome. A. Hypotrichosis in Hypotrichosis-lymphedema-telangiectasia syndrome. B. Skin ulcers and thickening with scrotal edema in Prolidase deficiency. C. Reticular pigmentation in OL-EDA-ID syndrome. D. Redundancy of skin folds in Noonan syndrome. E. Inverted nipples in CDG Type I syndrome. Also see Figure 1D. Hairless cicatrix scalp defect in Aplasia cutis congenita-intestinal lymphangiectasia and Figure 6F for hirsutism in Persistent mullerian derivatives syndrome. Reproduced with permission from Am. J. Hum. Genet. [A (18)]; J. Ped. [B (127)]; Am. J. Med. Gen. [C (121), D (112)]; J. Med. Gen. [E (123)].*

and X-linked inheritance in 3 of 10, and appears in 9 of 10 syndromes of congenital onset lymphedema.

Ocular coloboma is a congenital abnormality from defective closure of the embryonic fissure of the optic cup. The defect is typically located in the lower part of the iris and occurs as a feature in many other multiple congenital anomaly (MCA) syndromes. Association of this anomaly with irregular patterning or pigment of the iris perhaps relates to an abnormal closure of the embryonic fissure with irregular or excessive migration of neural crest cells into the iris stroma (96).

Conjunctival edema *(Fig. 2A,F)* or conjunctival vascular malformations

appeared in some syndromes, and sometimes it was thought to develop from a carotid-cavernous fistula or from increased perme-ability of conjunctival microvessels. In eight of the syndromes, where it was noted in most patients, 3 had visceral lymphangiectasia (2 intestinal; 1 pulmonary) and 2 had inborn errors of metabolism.

Eyelid ptosis *(Fig. 2A-C)*, or droopy eyelid, is seen in many syndromes. A neurogenic form is thought to arise from innervational defects during embryonic development whereas a mechanical type has been described with excessive weight of the eyelid from edema. An involutional variant has been attributed to degeneration of the muscle-to-eyelid attachments. Finally, there
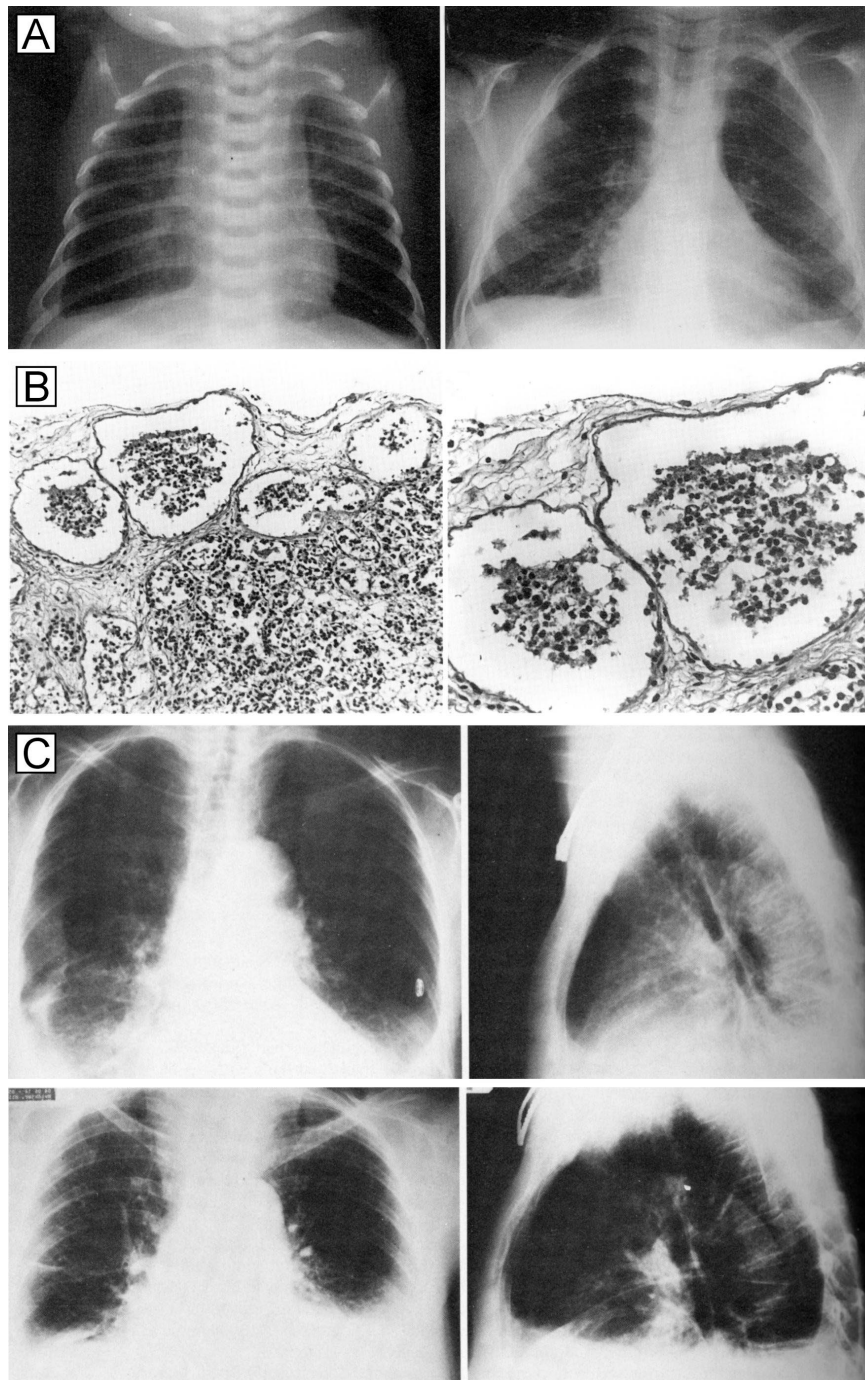
Fig. 8. Pulmonary Manifestations in Hereditary Lymphedema Syndromes. A. Progression of pulmonary changes on radiographs in Njolstad syndrome (congenital pulmonary lymphangiectasia) with pleural effusions, interstitial edema, and increased pulmonary vasculature. B. Lymphangiectasia on post-mortem lung section in Njolstad syndrome. C. Pleural effusions on radiographs in Yellow nail syndrome. Reproduced with permission of Euro. J. Ped. [A,B (131)]; Acta Med. Scand. [C (132)].
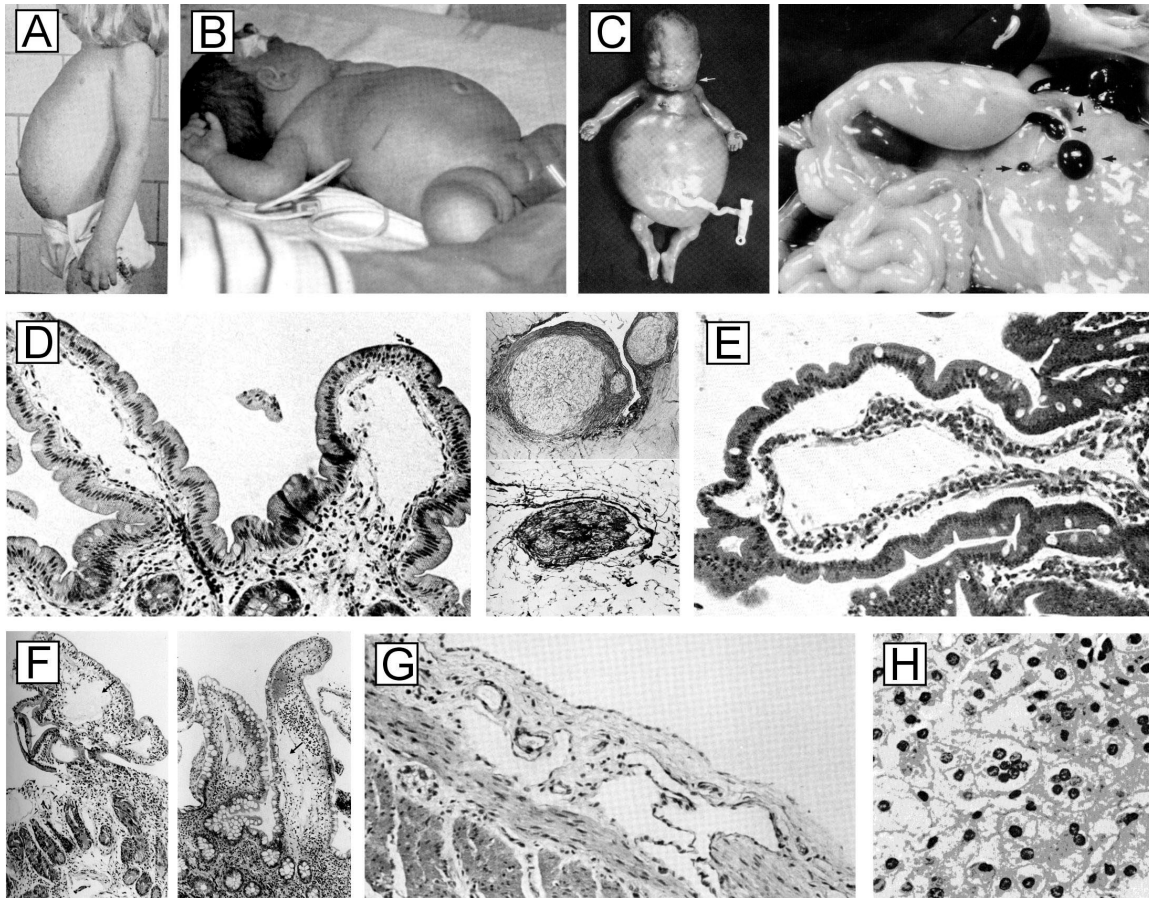
*Fig. 9. Gastrointestinal/Hepatic Abnormalities in Hereditary Lymphedema Syndromes. A. Chylous ascites and umbilical hernia in a child with Chylous ascites, autosomal recessive type, syndrome. B. Abdominal distention with ascites in Persistent mullerian derivatives with intestinal lymphangiectasia. C. Abdominal distention, ascites and polysplenism in Campomelia, Cumming type. D-F. Dilated lacteals and lymphangiectasia on intestinal tissue section in Autosomal dominant intestinal lymphangiectasia (D), Noonan syndrome (E), and Hennekam syndrome (F). G. Microscopy of small intestine with numerous dilated lymphatics on the serosal side of the muscularis propria. H. Dilated bile canaliculi and multinucleate hepatic parenchymal cells in liver tissue section in Aagenaes syndrome. Reproduced with permission from J. Ped. [A (59), D (134), E (90)]; Am. J. Med. Gen. [B,G (81), C (124), F (135)]; Gastroenterology [D (133)]; Arch. Dis. Child. [H (137)].*

are rare examples of congenital myogenic ptosis, where the eyelid muscles are either scarred or functionless. There is also a classification of patterns which show a genetic basis: 1) simple ptosis, due to failure of peripheral differentiation of muscles, transmitted as a dominant; 2) ptosis with blepharophimosis, also due to faulty peripheral differentiation and transmitted as a dominant; 3) ptosis due to ophthalmoplegia usually of central origin; 4) ptosis associated with myasthenia gravis and myotonia (both rare as congenital disorders); 5) ptosis due to congenital sympathetic palsy; 6) synkinetic ptosis; and 7) intermittent pseudo-ptosis associated with the retraction syndrome (97). Linkage has been shown for two forms of hereditary congenital ptosis near lp34.l-p32 and Xq24-27.1 (98). Another syndrome (Blepharophimosis, Epicanthus inversus, and
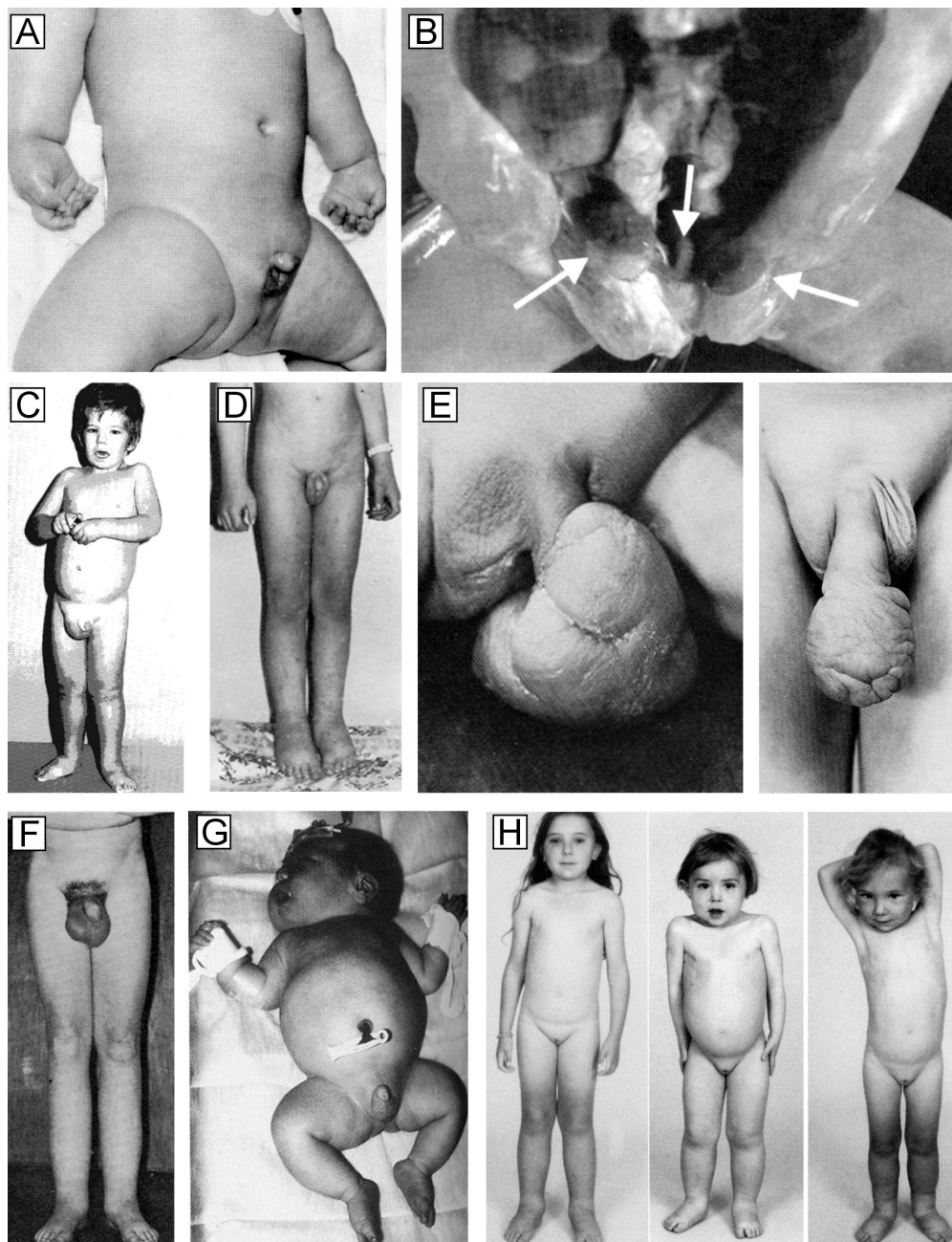
*Fig. 10. Genital Abnormalities in Hereditary Lymphedema Syndromes. A. Hypogonadism and cryptorchidism in Nevo syndrome. B. Mixed gender genitalia with two testes (left and right arrows) and uterus (upper arrow) in Persistent mullerian derivatives with intestinal lymphangiectasia. C. Genital and lower extremity lymphedema in Aplasia cutis congenita-intestinal lymphangiectasia D. Shawl scrotum and peripheral lymphedema in Aarskog syndrome. E. Hypertrophy of prepuce in sibs with congenital recessive lymphedema (Mucke syndrome) F. Scrotal lymphedema in Aagenaes syndrome. G. Micropenis and cryptorchidism in Persistent mullerian derivatives syndrome. H. Vulvar and labial edema in Njolstad syndrome. Reproduced with permission from Am. J. Med. Gen. [A (136), B,G (81), H (109)]; Am. J. Dis. Child. [C (77)]; J. Med. Gen. [D (110)]; Eur. J. Ped. [E (93)]; Arch. Dis. Child. [F (137)].*

Ptosis-BPES, Type I and II) has documented mutations in the forkhead transcription factor, *FOXL2*, which is selectively expressed in the mesenchyme of developing mouse eyelids and in adult ovarian follicles (99). This finding is of particular interest because another syndrome associated with ptosis is lymphedema-distichiasis, where documented mutations have been consistently identified in another (but possibly similar acting) forkhead transcription factor, *FOXC2* at 16q24.3; however, only some patients have ptosis (5,14,100).

Congenital glaucoma is thought to result from increased intraocular pressure dating from intrauterine life The canal of Schlemm is intact and communicates normally with the venous system, as demonstrated by filling of the canal with blood when the jugular veins are compressed. The defect is thought to involve increased permeability of the trabeculum to aqueous humor. Autosomal recessive inheritance is the major inheritance pattern in isolated congenital glaucoma and in the three associated LE-AD syndromes, it also segregates in an autosomal recessive pattern. In addition, LE-AD syndromes with reported congenital glaucoma also displayed visceral lymphangiectasia (2 pulmonary; 1 intestinal). Mutations have also been identified in several genes for cytochrome P450 (2p21), myocilin (trabecular meshwork-induced glucocorticoid response protein) (1q24.3-q25.2), *LIM* homeo box transcription factor 1, ß (9q34.1). *FOXO1* (13q14.1) and *FOXC1* (6p25), both forkhead transcription factors, have been linked to several syndromes with anterior eye segmental defects including the Axenfeld-Reiger group of anomalies (19). Of particular interest, *FOXO1*, also has a processed pseudogene that maps to 5q35.2-q35.3 (19). Here, several genes have been implicated in a seemingly heterogenic disorder suggested by a variety of chromo-somal abnormalities including deletions of 13q14, deletion of chromosome 10, pericentric inversion of chromosome 6, and isochromo-some of 6q as reviewed by Phillips et al (102).

Congenital or familial cataracts are associated with many syndromes but noted in only two LE-AD syndromes. Hejtmancik et al (103) presented a table of 9 loci implicated in nonsyndromal cataracts and mapped to specific chromosomal sites. Epicanthal folds *(Fig. 2E)* and slanted palpebral fissures *(Fig. 3I)* are other derangements described in several multiple congenital abnormality (MCA) syndromes and chromosomal aneuploidies.

Distichiasis is found not only in human *FOXC2* haploinsufficiency but also in *Foxc2* haploinsufficient mice (104).

*Dysmorphic Facies (Figs. 3A-I, 4A-D, References 78,93,105-112, Tables 2-4)*

Dysmorphic facial features are characteristic of most MCA syndromes, and specifically have been described in 20 of 36 LE-AD syndromes (56%). The most common anomalies are broad or flat nasal bridge *[n=12]*, hypoplastic, deformed, and/or low-set ears *[10]*, cleft palate or high-arched palate *[8]*, micrognathia *[7]*, abnormal philtrum/thin upper lip *[5]*, hypertrophied alveolar ridges or dental anomalies *[5]*, and mandibular hypoplasia *[4]*. *(Figs. 3A-I, 4A-D)*. Opitz (1) proposed a phenotype that he termed a "congenital lymphedema face" that included features such as hypertrophied alveolar ridges, redundant neck skin, depressed supracilliary areas, epicanthus, down-slanting palpebral fissures, broad nasal bridge, anteverted nostrils, retrognathia, and low-set ears. These phenotypic features may be the result of intrauterine edema disrupting the migration of tissues during embryonic development (112). However, not all patients with congenital lymphedema display these characteristics, and some of these features occurred *[5]* where the lymphedema was of late-childhood or adolescent onset.

Cleft palate is also common in many MCA syndromes with various inheritance patterns. Division of clefts of the face into those that include the secondary palate only

(the posterior or soft palate) and those that involve the primary palate and encompass clefts of the lip with or without the palate is probably valid, not only on a genetic basis, but also on embryologic constructs because the primary and secondary palates form independently (113). Isolated cleft palate has been linked to chromosome 2q32 (114) and chromosome 6p24.3 (115). Several mutations in the *TBX22* gene (Xq12-q21) have been described in X-linked cleft palate and ankyloglossia (116). The gene encodes a protein that belongs to a family of transcription regulators that share a common DNA-binding domain, the T-box. Another mutation in a homeobox gene *HOX7* (also called *MSX1*) is a candidate gene for human cleft palate (117). Kaartinen et al (118) found another candidate gene *TGF-ß3* at 14q24, and in their *Tgf-b3*-null mutant mice defective palatogenesis was accompanied by a consistent delay in pulmonary development. They suggested an essential function for TGF-ß3 in normal palate and lung morphogenesis and implicated this cytokine in epithelial-mesenchymal interaction. In addition to the above mutations, patients with lymphedema-distichiasis syndrome, caused by a mutation in the forkhead transcription factor *FOXC2*, occasionally exhibit cleft palate, and *Foxc2* knockout (-/-) mice are uniformly born with a cleft palate (119). In addition, Hereditary Lymphedema, Type II or Meige disease also occurs with adolescent-onset lymphedema and cleft palate (107). Of note, among all patients with palatal abnormalities and LE-AD syndromes, none had cleft lip.

Hypertrophied alveolar ridges, noted in 5 LE-AD syndromes *(Fig. 3B)*, are often a major feature of other MCA syndromes. One of these, Robinow syndrome, has been linked to mutations in a receptor tyrosine kinase-like orphan receptor 2 on 9q22 (120).

*Skeletal/Torso Anomalies (Figs. 5A-D, Fig. 6A-G, References 75,80,88,106,109,110,121-125, Tables 2-4)*

Thoracic and vertebral anomalies have been described in 17 of 36 (47%) of LE-AD syndromes including pectus excavatum *[n=7]* scoliosis/kyphosis or vertebral anomalies *[6]*, widely-spaced or inverted nipples *[5]*, and various rib anomalies *[2] (Fig. 5A-D)*. Familial scoliosis/kyphosis is well recognized in both idiopathic and syndromic forms, and the etiology is considered multifactorial and complex. Widely-spaced nipples is a feature in 15 other OMIM-listed syndromes and inverted nipples in 9. Pectus excavatum is featured in more than 50 OMIM-listed syndromes and in isolated familial reports with an autosomal dominant inheritance (61). Lymphedema-distichiasis patients exhibit a variety of rib and vertebral abnormalities (15,100) as do *Foxc2* knockout (-/-) mice (119).

Bony or limb abnormalities have been reported in 13 of 36 LE-AD syndromes (36%) including malformation of digits (polydactyly, clinodactyly, or short, broad, or spindle shaped) *[n=12]*, syndactyly *[6]*, small hands and feet *[4]*, or disproportionate limb length *[3] (Fig. 6A-G)*. In three forms of hereditary campomelia, several mutations in *SOX9* (SRY-related HMG box) (17q24.3-q25.1) have been identified. Studies of the mouse *Sox9* during embryogenesis have demonstrated that the gene is expressed predominantly in mesenchymal condensations throughout the embryo (126).

*Growth Defects*

The most frequent growth abnormality was growth retardation or short stature, which occurred in 17 of 36 (47%) LE-AD syndromes, with osteopenia in 3 of these 17. One additional syndrome featured overgrowth as a major feature.

*Integumental/Joint Defects (Fig.7A-E, References 18,112,121,123,127, Tables 2-4)*

Specific joint abnormalities reported in more than two LE-AD syndromes were contractures *[n=3]* and clubfoot *[5]*

*(Fig. 6C,G)*. Both joint malformations have been associated with oligohydramnios, but 40% of prenatally documented cases of oligohydramnios had other anomalies or family history that could explain the malformations (128). Our review of reported pregnancy complications in LE-AD found that polyhydramnios occurred commonly in 6 LE-AD syndromes but not oligohydramnios. A study of 287 clubfoot families showed that the best genetic model is a single dominant gene with a penetrance of 33% and a predicted gene frequency of 0.9% (129). In 3 of 5 LE-AD syndromes associated with clubfoot, consanguinity existed, a fourth (German syndrome) occurred exclusively in Ashkenazi Jewish patients, with the final LE-AD report occurring in an isolated patient.

Nail dysplasia *(Fig. 6D)* and/or abnormal dermal patterning occurred in 14 of 36 LE-AD syndromes (40%). In order of decreasing frequency they include simian crease, tibial creases, or absent skin creases *[n=6]*, hypoplastic or dysplastic fingernails and/or toenails *[5]*, abnormal dermal ridge patterning *[3]*. Simian crease is a major finding in Trisomy 21 and a few other ectodermal dysplasia syndromes also associated with abnormal dermatoglyphics and nail changes (19).

Specific skin/hair abnormalities were likely underreported/bias-reported with the assumption that several might be the result of underlying lymphedema *(Fig. 7A-E)*. Some distinction was raised between lower extremity lymphedema alone and lower extremity lymphedema frequently complicated by erysipelas or chronic ulcerations *(Fig. 7B)*. These complications occurred in 9 of the 36 LE-AD syndromes. Characteristic surface vascular marking were also described in 4 of 34 and altered skin pigment in 2 of 36 *(Fig. 7C)*. Hypotrichosis has been noted in Hypotrichosis-lymphedema-telangiectasia syndrome *(Fig. 7A)*, where mutations in the transcription factor *SOX18* have been identified (18).

## Cardiac Anomalies

Cardiac abnormalities occurred in 14 of 36 (39%) of LE-AD syndromes. Almost every congenital heart defect was described at least occasionally although the type varied even within syndromes and families. LE-AD syndromes with more than one type of cardiac abnormality included Noonan syndrome associated with Lymphedema [atrial (ASD) or ventricular septal defect (VSD), valvular dysplasia, and hypertrophy], Campomelia, Cumming-type (ASD, total anomalous pulmonary venous return, pericardial effusion), Lymphedema-microcephaly-chorioretinopathy syndrome (ASD, VSD, Right Aortic Arch), Lymphedema-ASD [ASD, Patent Ductus Arteriosus (PDA)], Mucke syndrome (PDA, Coarctation of the Aorta), and Lymphedema-distichiasis [Tetralogy of Fallot (or any of its component defects such as VSD and aortic arch defects as also seen uniformly in *Foxc2* (-/-) mice (119), mitral valve prolapse]. Pericardial effusions were noted in two syndromes, and in one of these, Hennekam syndrome, pericardial lymphangiectasia was documented (130).

## Pulmonary Anomalies *(Fig. 8A-C, References 131-132, Tables 2-4)*

Pulmonary function abnormalities were documented in 12 of 36 LE-AD syndromes (39%). Seven syndromes reported recurrent chylothorax or pleural effusion and of these, three had documented pulmonary lymphangiectasia *(Fig. 8A-C)*. Two additional syndromes with histologically proven pulmonary lymphangiectasia did not report chylothorax. However, pulmonary lymphangiectasia has historically been hard to corroborate at autopsy with collapse of the lung after death. Other clinical findings reported in syndromes without documented structural abnormalities were acute respiratory distress *[n=3]*, obstructive/restrictive lung disease *[1]*, and primary pulmonary hypertension *[2]*.

*Gastrointestinal Anomalies (Fig. 9A-H, References 59,81,90,105,124,133-136, Tables 2-4)*

Gastrointestinal abnormalities were frequently reported in LE-AD syndromes (19 of 36 or 53%). Twelve of nineteen had visceral lymphangiectasia in addition to peripheral lymphedema as a major component of the symptom complex, and in seven it was documented as intestinal lymphangiectasia *(Fig. 9D-G)*. The remaining LE-AD syndromes *[n=7]* each reported only one gastrointestinal abnormality compared with those with visceral lymphangiectasia which on average reported 2.7 anomalies. Bias may be a confounding factor as other anomalies in the predominantly involved organ system are more likely to be described or evaluated; however, in two syndromes where intestinal lymphangiectasia was the major feature it was described as an isolated phenomenon. Intrahepatic bilary tract abnormalities were noted in Aagenaes syndrome *(Fig. 9H)*. Autosomal recessive inheritance was the most common pattern *[7 out of 10]* in syndromes associated with visceral organ involvement.

*Genitourinary Anomalies (Fig. 10A-H, References 77,81,92,93,109,110, Tables 2-4)*

Genitourinary anomalies were reported in 21 of 36 LE-AD syndromes (58%). In four the only finding was edema of the genitalia *(Fig. 10C,F,H)*. In the remaining 17, an average of 2.2 abnormalities were reported. Structural defects of the kidney were reported in 5 of 17 and renal insufficiency in 4 of 17. Genital edema was combined with another abnormality in 7 of 17 Hemaphroditism was seen in Persistent mullerian derivatives syndrome *(Fig. 10B)*, cryptorchidism *(Fig. 10A)* in 8 of 17, hydrocele in 5 of 17, micropenis *(Fig. 10G)* in 4 of 17, hypospadias in 2 of 17, and hyperplasia of scrotum ("shawl scrotum") *(Fig. 10D)* or penis *(Fig. 10E)* in 2 of 17. In addition, genital organ (testicular) lymphangiectasia occurred

in a patient with Noonan syndrome and lymphedema.

*Immunodeficiency*

Immune dysfunction was documented in 12 of 36 LE-AD syndromes (33%) although three were associated with intestinal lymphangiectasia (IL) and protein-losing gastroenteropathy as well as intestinal malabsorption. The following were reported in 9 LE-AD syndromes not accompanied by intestinal lymphangiectasia; splenomegaly *[n=5]*, IgG deficiency *[3]*, and hyperimmuno-globulinemia (IgG) in two. Three syndromes with IL had IgG deficiency *[2]*, lymphopenia *[3]*, and skin anergy *[1]*. One syndrome (OL-EDA-ID) with immune dysfunction as a major feature has been mapped to chromosome Xq28 uncovering a documented mutation in *NEMO*, a protein involved in the NFkß signaling pathway (138,139).

*Blood Vascular Anomalies and Hematological Abnormalities/Malignancies*

Blood vessel and/or hematological findings were noted in 14 of the 36 LE-AD syndromes (38%). Malignancies occurred in 6 of 34 (16%). The hematological findings included various blood vascular abnormalities (placental villous edema and chorioangioma, single umbilical artery, venous varicosities, and hypoplasia of pelvic veins) *[n=8]* plus coagulopathy *[3]*, anemia *[3]*, thrombocyto-penia *[3]*, and telangiectasia *[1]*. Of the malignancies, one or two occurred in 5 syndromes; however, in Yellow nail syndrome more than 6 different malignancies were reported.

*Gender Ratio*

Although females are more commonly affected in the two most common hereditary LE-AD syndromes, namely, Milroy and Meige, our review showed that males were affected more often than females in 18 of the
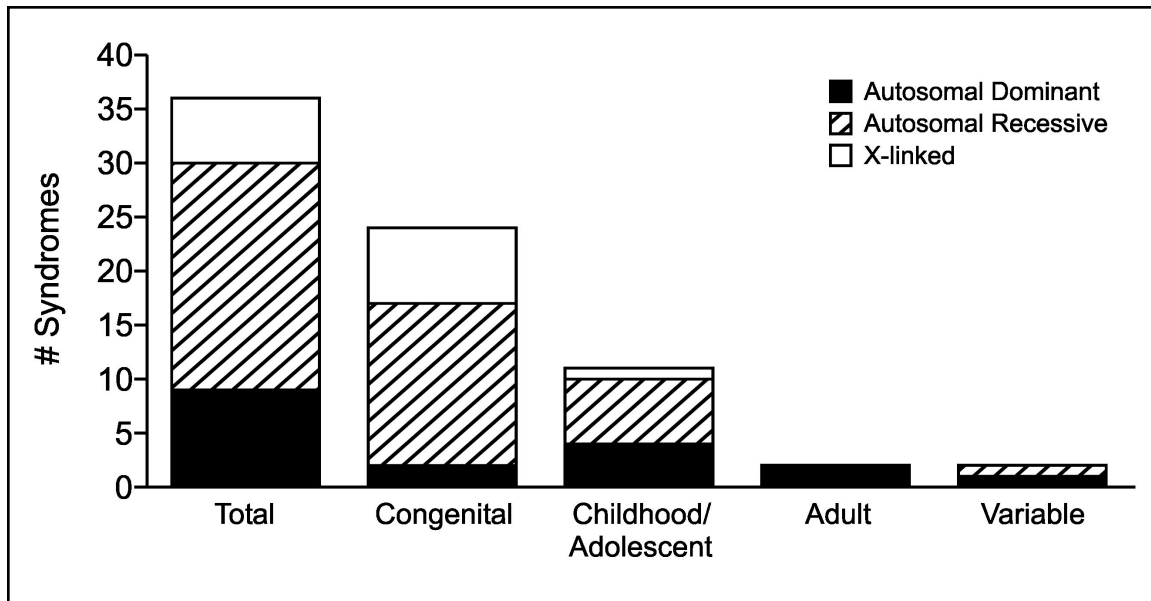
*Fig. 11. Inheritance Patterns and Age of Onset in Hereditary Lymphedema Syndrome.*

syndromes where the gender ratio was significant (greater than a 2 to 1) and in 10 of these only males were affected. Four of these ten were classified as X-linked inheritance pattern. Five LE-AD syndromes showed a significant female predominance (greater than 2:1 ratio); in three of these, only females were reported and in another only females survived to term. Of interest, the variant form of tuberous sclerosis was reported in only females, showed autosomal recessive inheritance and only unilateral left lower extremity edema.

*Pregnancy*

Pregnancy histories were available in limited numbers and reviewed. Of those available common findings were polyhydraminos *[n=6]*, cystic hygroma *[4]*, hydrops fetalis *[2]*, stillbirths or multiple miscarriages *[2]*, and maternal edema *[2]*.

*DISCUSSION*

Despite major advances in understanding of (hem)angiogenesis driven by interest in its role in the development of cardiovascular anomalies and dysfunction as well as in the growth of cancer, physiologic insight into lymphatic vascular disorders and dysfunction has lagged far behind in part due to technical difficulties in visualizing lymphatics and assessing their function, lack of well-described phenotypic abnormalities in families with hereditary disorders, paucity of experimental transgenic animals, and elusiveness of distinctive lymphatic-specific molecular markers. Recent recognition that VEGF-C and VEGF-D and their receptor, VEGFR-3, are intimately involved in lymphatic growth and development (140,141) has led to a surge of interest in lymphangiogenesis. Indeed, the first gene mutation identified in a family with Milroy disease, was the gene for the VEGFR-3 endothelial cell receptor. A second LE-AD syndrome (OL-EDA-ID) with congenital-onset lymphedema, X-linked inheritance, multiple congenital anomalies, abnormal bone growth, and immunodeficiency was also found to be due to a defect in VEGF signaling (139).
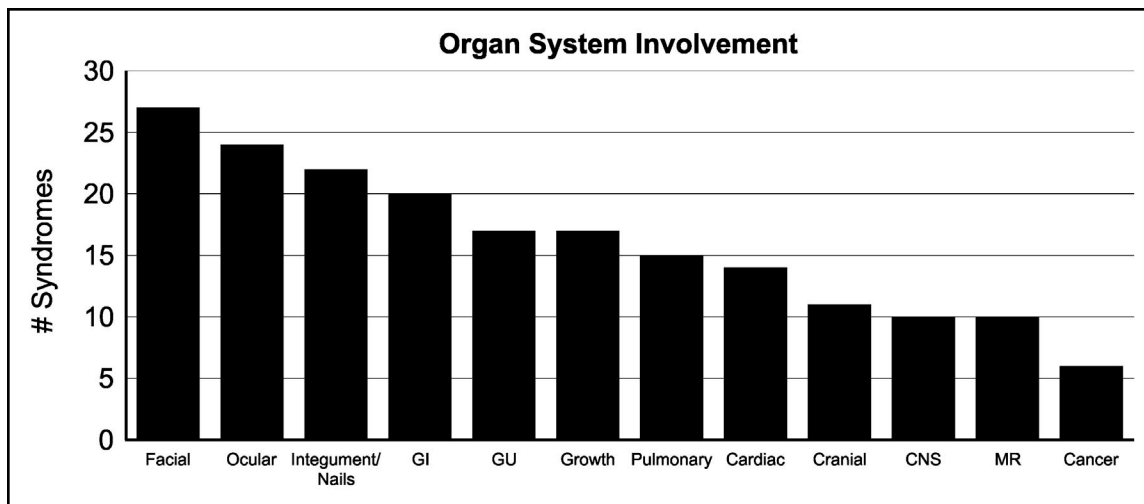
By amalgamating these numerous

**Organic System Involvement**



*Fig. 12. Organ System Involvement (in declining order) in Hereditary Lymphedema Syndromes. See text for further details.*

published case reports and case histories presented in a multitude of conferences over several decades, into one source, we endeavored to enable practitioners and investigators to delineate more easily the common and distinctive phenotypic findings. Detailed description and improved syndromic classification should, in turn, help in identifying specific gene loci that ultimately are responsible for these seemingly disparate and unconnected clinical patterns. Moreover, whereas numerous angiogenic and vasculogenic factors are being uncovered in blood and lymph vascular growth development, it is likely that the expression and regulation of other molecular events are responsible for the spectrum of malformations phenotypically manifest in lymphangiodysplastic disorders.

Mutations in transcription factors have historically been associated with multiple congenital anomalies. For example, as mentioned earlier, a mutation in *FOXC2*, a transcriptional factor expressed in a variety of embryonic mesenchymal tissues, has been described in more than 33 families with lymphedema-distichiasis (pubertal onset peripheral lymphedemas with double row of eyelashes). Several members of these families

also manifest congenital cardiac defects (e.g., Tetralogy of Fallot), cleft palate, webbed neck, bony abnormalities, and other ocular defects (15,100).

During embryogenesis, vascular growth factors and receptors impact organs and tissues other than the cardio(blood-lymph)vascular system. Moreover, in several of the LE-AD syndromes, organs derived and lymph emanating from these tissues are often affected clinically where they share embryologic tissue origins. Exploration of these molecular pathways in the future and of their role in development of other tissues should provide insight into the still ill-defined processes of normal and abnormal development and growth of the blood and lymph vasculatures. For this to occur, it is critical that phenotypes be accurately and fully characterized by refined imaging (lymphangioscintigraphy, magnetic resonance, computer tomography) and molecular methodology (genomics, proteomics), which are not yet commonly used in the clinical arena. By classifying patients correctly and more precisely (including ocular, limb, and dysmorphic features and anomalies, etc.), one can begin to coordinate the activities of

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multiple specialists such as pediatricians, perinatologists, dysmorphologists, geneticists, vascular surgeons, and plastic surgeons, with the primary care physician and other health care professionals so that molecular advances in basic lymphology can be translated into the clinical arena to benefit our patients.

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