X-linked Malformation and Infantile Lethality Syndrome (provisionally named Ogden Syndrome)

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Abstract (100-150 words)

This is a lethal X-linked disorder of infancy comprising a distinct combination of distinctive craniofacial features producing an aged appearance, growth failure, hypotonia, global developmental delays, cryptorchidism, and acquired cardiac arrhythmias. The first family was identified in Ogden, Utah, with five affected boys in two generations of family members. A mutation was identified as a c.109T>C (p.Ser37Pro) variant in *NAA10*, a gene encoding the catalytic subunit of the major human N-terminal acetyltransferase (NatA). This same mutation was identified in a second unrelated family, with three affected boys in two generations. This X-linked Malformation and Infantile Lethality Syndrome has provisionally been named Ogden Syndrome, in honor of the hometown where the first family resides.

5-10 chapter keywords

lethal X-linked disorder of infancy

aged appearance

N-terminal acetylation

NAA10, a gene encoding the catalytic subunit of the major human N-terminal acetyltransferase NatA

post-translational modification

b. Chapter summary

There are two unrelated families thus far discovered with a lethal X-linked disorder of infancy comprising a distinct combination of an aged appearance, distinctive craniofacial features, growth failure hypotonia, global developmental delays, cryptorchidism, and acquired cardiac arrhythmias (see **Figure 1**) [1]. X-chromosome exon sequencing and a probabilistic disease-causing variant discovery algorithm identified in these two families the same c.109T>C (p.Ser37Pro) variant in *NAA10*, a gene encoding the catalytic subunit of the major human N-terminal acetyltransferase (NatA). The absence of this variant in controls, the amino acid conservation of this region of the protein, the predicted disruptive change, and the co-occurrence in two unrelated families with the same rare disorder suggest that this mutation is necessary for expression of the phenotype. There is significantly impaired biochemical activity of the mutant hNaa10p, suggesting that a reduction in acetylation of some unidentified proteins by hNaa10p might lead to this disease. This is the first human genetic disorder identified resulting from impairment of N-terminal acetylation, one of the most common protein modifications in humans.

c. Gene description

NAA10, a gene encoding the catalytic subunit of the major human N-terminal acetyltransferase

(NatA), OMIM entry #300855 for Ogden Syndrome, with alternative title N-terminal acetyltransferase Deficiency.

d. Clinical summary with composite figure

This is an X-linked condition affecting males and characterized by postnatal growth failure with developmental delays and dysmorphic features characterized by wrinkled forehead, anterior and posterior fontanels, prominent eyes, largedown-slanting palpebral fissures, thickened or hooded eyelids, large ears, flared nares, hypoplastic alae nasi, short columella, protruding upper lip, and microretrognathia (see **Figure 1** and **Table 1**). There is also delayed closing of fontanels, and the boys also have broad great toes. Skin is characterized by redundancy or laxity with minimal subcutaneous fat, cutaneous capillary malformations, and very fine hair and eyebrows. Death resulted from cardiogenic shock following arrhythmia, which was noted in all affected individuals. Several of the boys had structural anomalies of their hearts including ventricular septal defect, atrial septal defect, and pulmonary artery stenosis. Arrhythmias at the time of death included torsade de pointes, premature ventricular contraction (PVC), premature atrial contraction (PAC), supraventricular tachycardia (SVtach), and ventricular tachycardia (Vtach). Most of the children had inguinal hernia, and the majority had, at least, unilateral cryptorchidism. All had neonatal hypotonia progressing to hypertonia, and cerebral atrophy on MRI; several, but not all, had neurogenic scoliosis. Death occurred prior to 2 years in all cases and prior to 1 year in the majority. There are extensive clinical details for each child reported in the original publication [1].

Table 1. Features of the syndrome	
Growth	**post-natal growth failure**
Development	**global, severe delays**
Facial	**wrinkled foreheads** **prominence of eyes, down-sloping palpebral fissures, thickened eyelids** **large ears** **flared nares, hypoplastic alae nasi, short columella** **protruding upper lip** **micro-retrognathia**
Skeletal	**delayed closure of fontanels** **broad great toes**
Integument	**redundancy / laxity of skin** **minimal subcutaneous fat** **cutaneous capillary malformations** **very fine hair and eyebrows**
Cardiac[a]	**structural anomalies (ventricular septal defect, atrial level defect, pulmonary artery stenoses)** **arrhythmias (Torsade de points, PVCs, PACs, SVtach, Vtach)** **death usually associated with cardiogenic shock preceded by arrhythmia**
Genital[a]	**inguinal hernia** **hypo- or cryptorchidism**
Neurologic[a]	**hypotonia progressing to hypertonia** **cerebral atrophy** **neurogenic scoliosis**
[a] features of the syndrome demonstrating more variability. Though variable findings of the cardiac, genital and neurologic systems were observed, all affected individuals manifested some pathologic finding of each.	

e. Molecular genetics

A mutation in an enzyme involved in N-terminal acetylation of proteins has thus far been associated with this distinct X-linked phenotype in two families (**Figure 2**), with 8 males who carried the hypomorphic hNaa10p p.Ser37Pro allele dying in infancy with cardiomegaly and cardiac arrhythmias. N-terminal acetylation is one of the most common protein modifications in humans, occurring on approximately 80% of all human proteins [2]. It is catalyzed by several distinct NAT-enzyme complexes, of which the major one is the NatA complex [3]. The catalytic subunit of the NatA complex, hNaa10p, is essential for survival in the organisms *Drosophila melanogaster* [4], *Trypanosoma brucei* [5] and *Caenorhabditis elegans* [6]. It is presumed that an amorphic (a null) *NAA10* mutation would lead to embryonal lethality in humans, although this has not been proven.

f. Diagnosis and Management

The diagnosis is made by molecular diagnosis in male infants with the characteristic facial appearance, postnatal growth failure and developmental delays. The full spectrum of Ogden syndrome is yet to be described, and the phenotypic spectrum will likely expand as other mutations in *NAA10* or other NATs are found. As the affected infants have an aged appearance, the differential diagnosis should include Hutchinson-Gilford progeria syndrome and other progeroid syndromes. However, the autopsies did not reveal any premature arteriosclerosis or degeneration of vascular smooth muscle cells (SMCs), as is seen in Hutchinson-Gilford progeria syndrome (MIM #176670) [10],[11].

To date, screening and interventions for individuals affected with Ogden syndrome has been largely empiric and without proven benefit to prolonging lifespan. That being said, quality of life is likely improved by taking some measures.

Neuroimaging has been obtained in a number of these children, primarily to screen for brain anomalies associated with their hypotonia and growth failure. In some cases, there was

an incidental finding of cerebral atrophy, but there was no radiographic evidence to explain their hypotonia or growth failure.

Baseline echocardiography is recommended as septal defects have been identified in several cases. Medical (pharmaceutical) management has been employed to slow the progression of congestive heart failure (CHF). Electrocardiography (EKG) is also obtained at the time of diagnosis, as fatal dysrhythmias develop with time and eventually lead to the boys' demise. In several cases, the initial EKG has been normal, with evolution of arrhythmias in the last months of life. It may be necessary to evaluate them on a monthly basis and be vigilant for signs of and symptoms of dysrhythmia/CHF. The arrhythmias have proven difficult to manage, though the full spectrum of anti-arrhythmics has not been tested. Individuals have responded to episodic cardioversion/defibrillation, but long term treatment has not yet been determined. There have been no attempts for more invasive interventions; such as the use of a pacemaker, implantable defibrillator or cardiac ablation.

Careful evaluation for umbilical and inguinal hernia is recommended, with herniorraphy suggested in cases where incarceration of the hernia appears likely.

In at least one individual, intervention for a neurogenic scoliosis was attempted with equivocal results. He did not respond to external bracing and rods were surgically placed. Unfortunately, he suffered a number of complications from this procedure and there was some doubt as to whether he truly benefitted from the therapy.

Dysphagia, gastroesophageal reflux and malnutrition from decreased caloric intake have been commonly observed. Feeding assistance *via* NG/NJ tube and antacids may be of some use. At least one of the affected infants responded well to Nissen fundoplication with a G-tube and relieved some of the burden of daily challenges for his parents.

Though attempted in order to identify a treatable component of their condition, extensive laboratory panels assessing digestive function, screening for metabolic decompensation and

hormonal dysregulation have not been significantly useful in improving the care or outcome for these children.

g. Molecular pathogenesis

N-terminal acetylation of proteins is catalyzed by N-terminal acetyltransferases (NATs). The primary NAT in terms of targeted substrates is the evolutionarily conserved NatA complex [2, 3, 12]. The functional impact of N-terminal acetylation remains elusive, but recent data suggest a role as a destabilization signal for proteins [13] and in the cellular sorting of nascent polypeptides [14]. The human NatA complex is composed of the catalytic subunit hNaa10p (hARD1) and the auxiliary subunit hNaa15p (NATH/hNAT1), both essential for its activity *in vivo* [15]. Increased NatA levels have been linked to tumor progression, and depletion of NatA subunits from cancer cells induces cell cycle arrest and apoptosis [16]. Human Naa10p is a protein of 235 amino acid residues, of which the first 178 residues compose a globular region, while the latter 57 residues are predicted to form an unstructured and flexible C-terminal tail [17]. Thus, Ser37 is located in a structured part of hNaa10p. For many soluble globular proteins, Pro is known to be potentially disruptive for secondary structure elements like the alpha-helix and beta-sheets [18]. Thus, although the structure of hNaa10p is undetermined, the p.Ser37Pro mutation may indeed affect the structure of hNaa10p and thereby the catalytic activity. Ser37 and its surrounding residues are highly conserved among eukaryotes [15], suggesting an essential function. A SIFT (Sorting Intolerant From Tolerant) analysis predicting whether an amino acid substitution affects protein function [19] strongly suggested that the substitution from Ser to Pro at position 37 would affect protein function [1]. Therefore, the published data show several things, including: 1) strong conservation of Naa10p Ser37, 2) a prediction of structural distortion by p.Ser37Pro, and 3) disruption of catalytic activity in the recombinant p.Ser37Pro protein *in vitro*. This implies that the hemizygous males with hNaa10p p.Ser37Pro might have impaired NatA function [1]. Thus, a number of protein N-termini might be insufficiently

acetylated, including Naa10 substrates that are both co- translationally and post- translationally acetylated (e.g., actins). The serious consequences of the p.Ser37Pro mutation therefore might be caused by the lack of N-terminal acetylation for one or several proteins requiring this modification for full functionality or for maintenance of adequate amounts in the cell. The effect of this mutation on specific pathways and cellular functions is still being determined, but theoretically, many functions could be involved. Since hNaa10p also has been suggested to perform N-lysine (N-epsilon) acetylation of proteins like beta-catenin [7], decreased N-lysine acetylation of selected substrates might also cause the observed effects. Finally, proposed non-catalytic functions of hNaa10p [8, 9] could be affected in the p.Ser37Pro mutant and thereby also play a role in the observed phenotypes.

3. Figures

Figure legends

Figure 1. Triptych of III-4 from Family 1. These pictures demonstrate the prominence of eyes, down-slanted palpebral fissures, thickened lids, large ears, flared nares, hypoplastic alae nasi, short columella, protruding upper lip and micro-retrognathia.

Figure 2. Pedigree drawing and Pictures of Families 1 and 2. A) Pedigree drawing for Family 1. SB, stillborn. Genotypes are marked for those in which DNA was available and tested. + is normal variant, mt is rare mutant variant. **B)** Pictures of five affected/deceased boys in this family, showing the aged appearance. **C)** Pedigree for Family 2. III-2 is the subject most well studied in the family. **D)** Pictures of II-I and III-2 in Family 2.

4. Additional online resources:

a. Additional clinical illustrations

See attached pictures.

b. Mutations

Currently, there are no other pathogenic mutations definitively identified in any of the other N-terminal acetyltransferase genes.

c. Additional Text.

We speculate that other mutations have not been discovered possibly due to embryonic lethality of such mutations.

h. References

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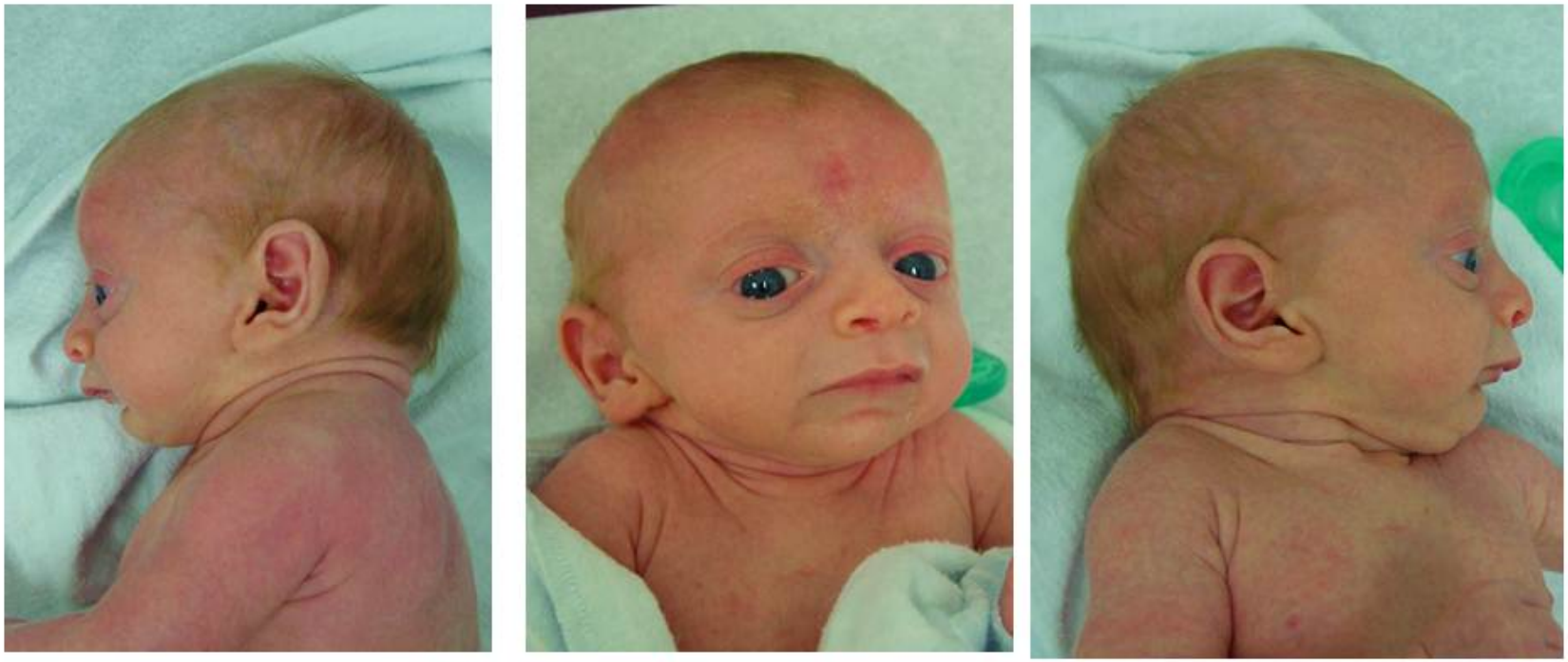
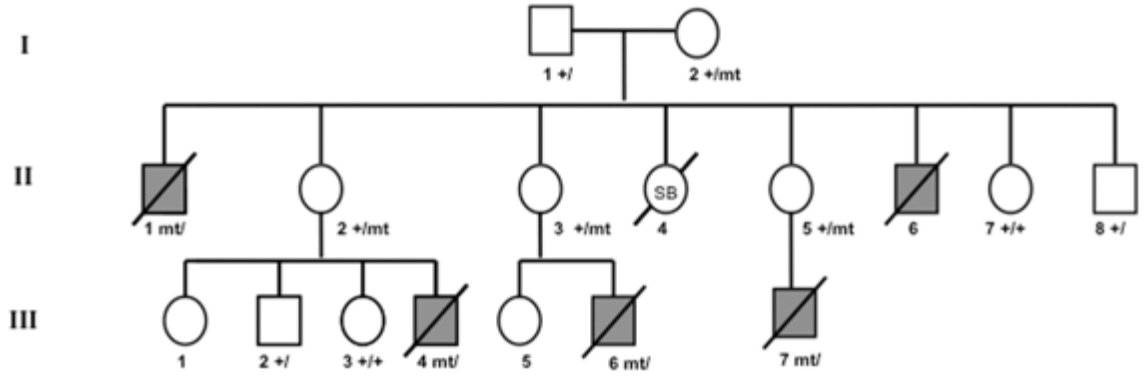


Figure 1. Triptych of propositus (Family 1 III-4).

A



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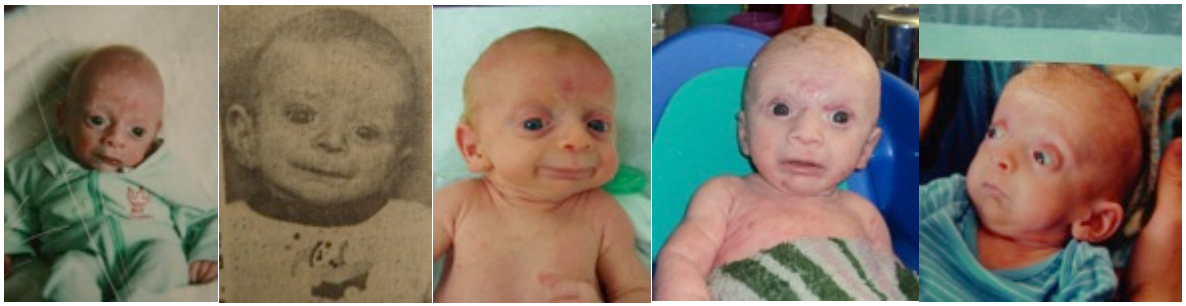
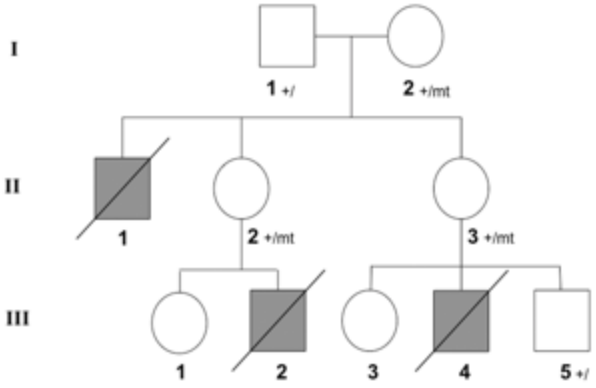


II-1 II-6 III-4 III-6 III-7

C



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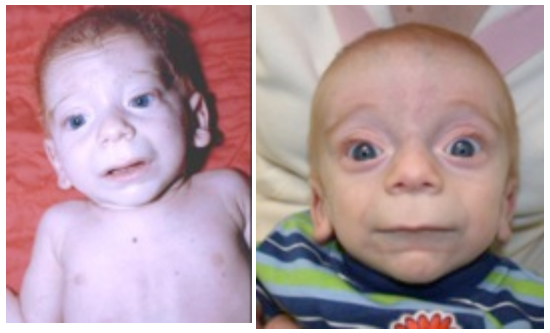
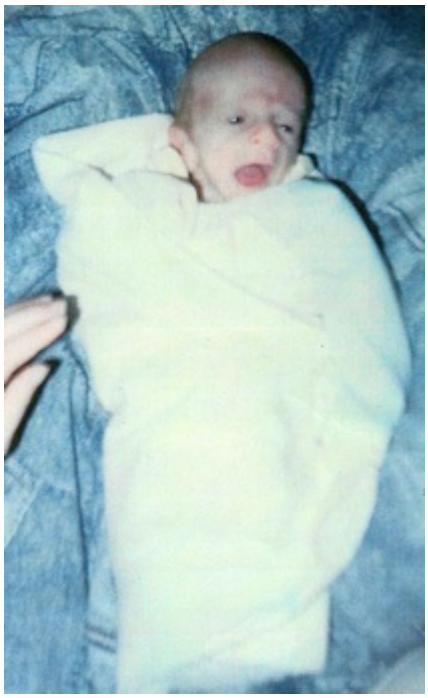
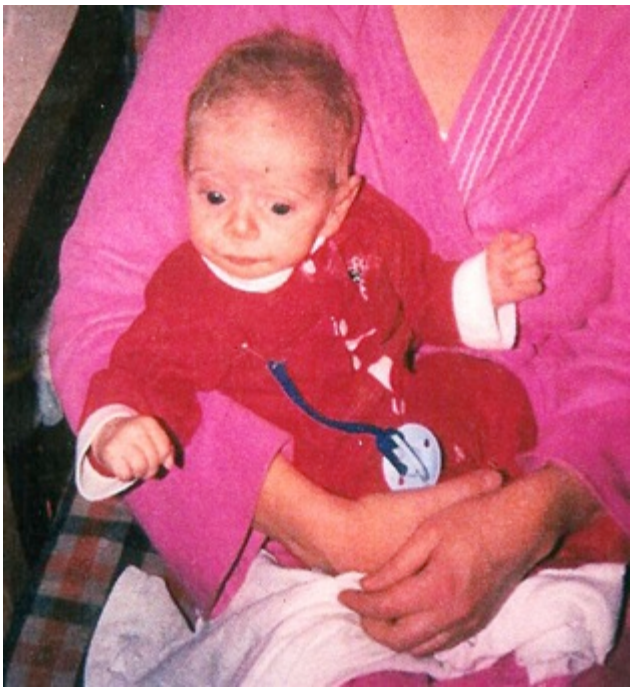


II-1 III-2

Family 1

Family 1: Individual II:1





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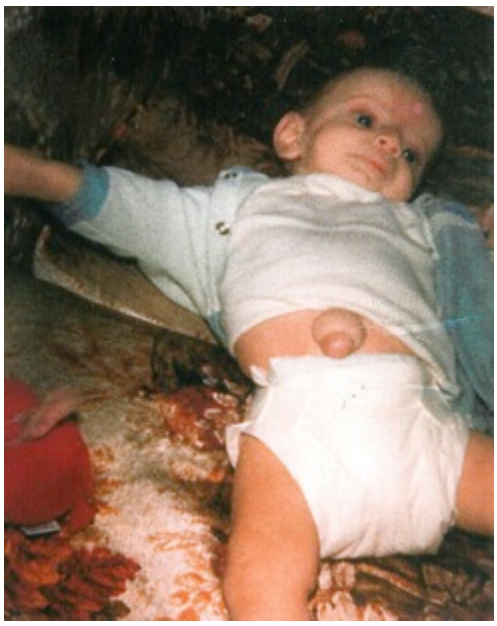

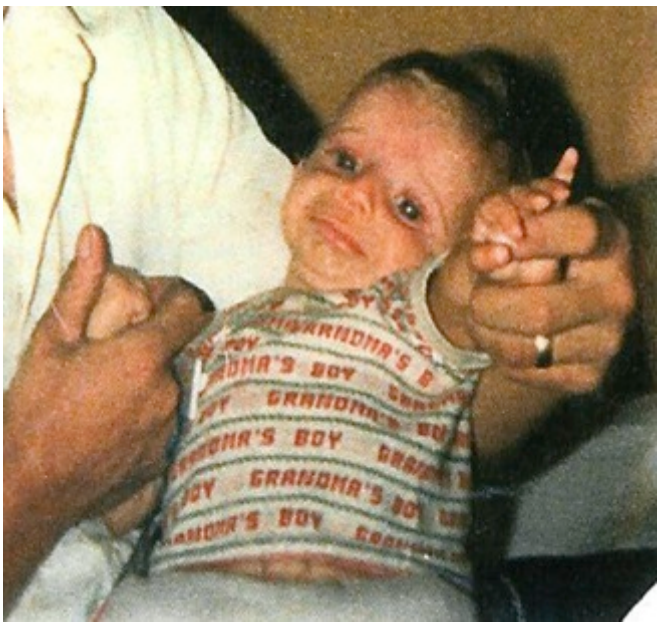

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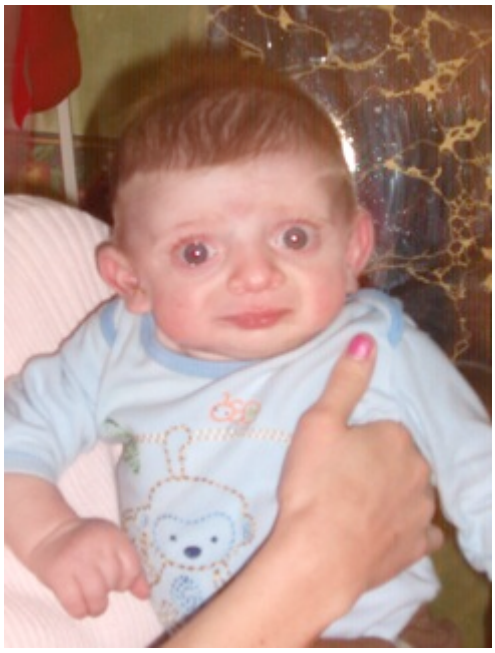

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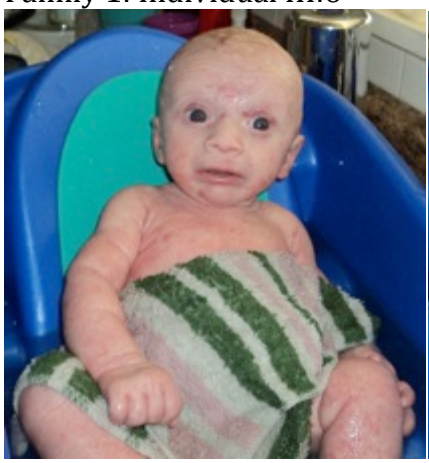
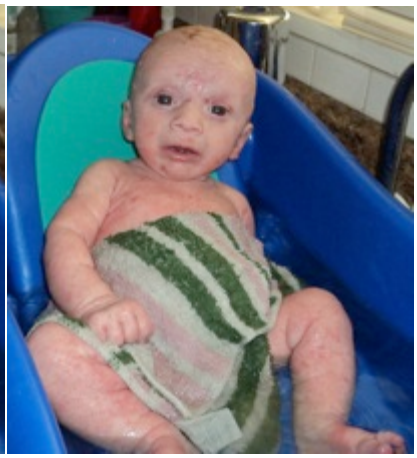
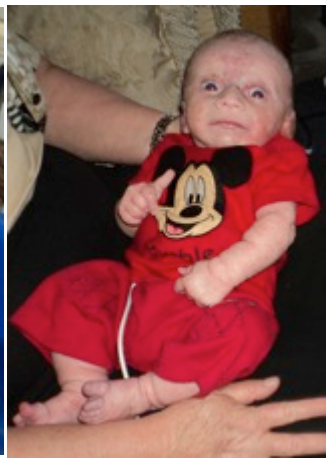
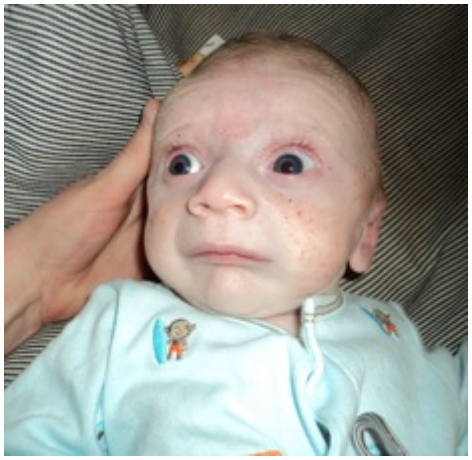
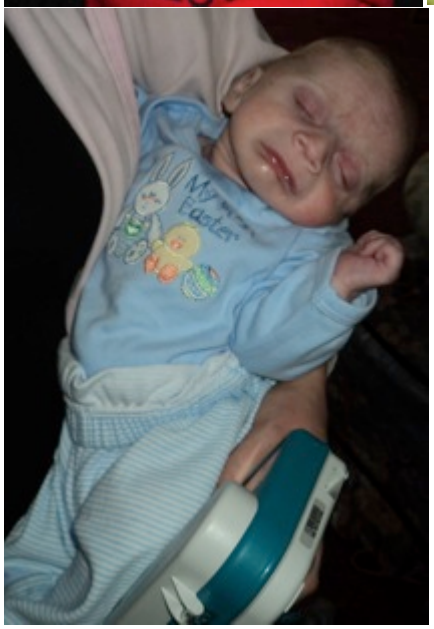




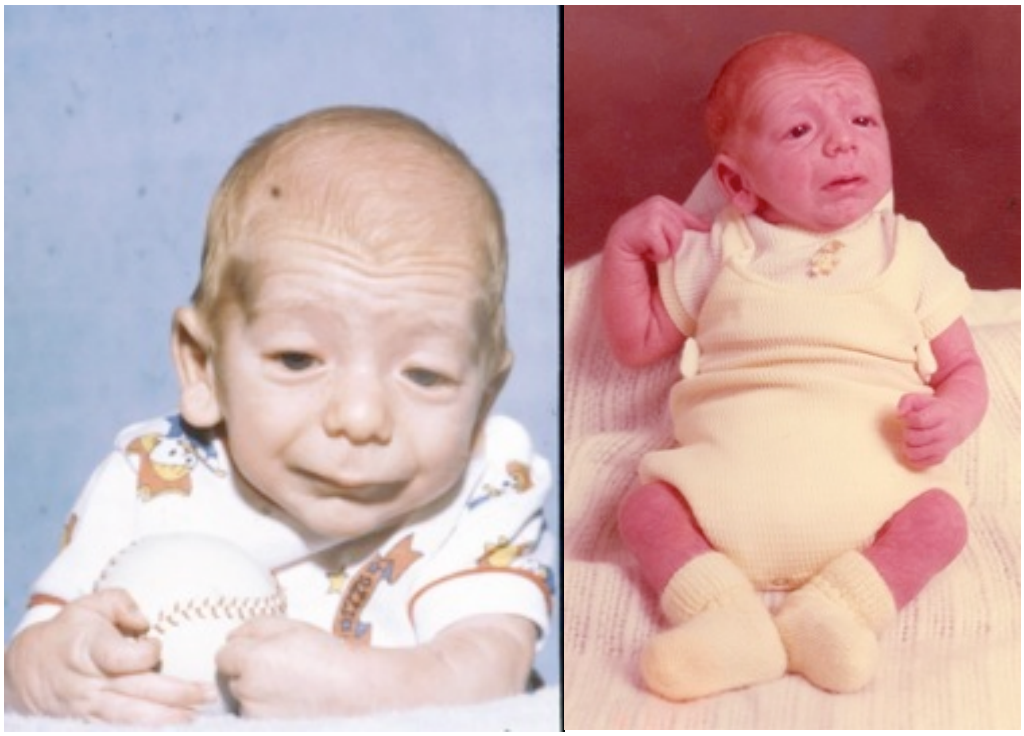




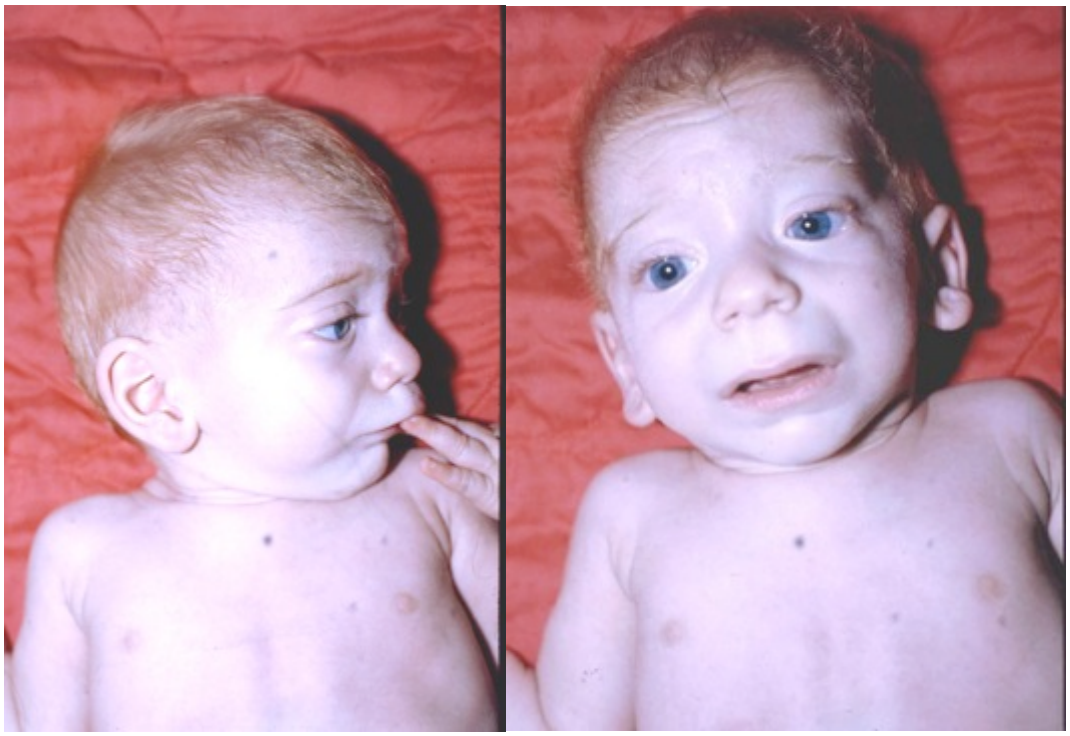
Family 1: Individual III:7

No additional pictures.

Family 2

Family 2: Individual II-1





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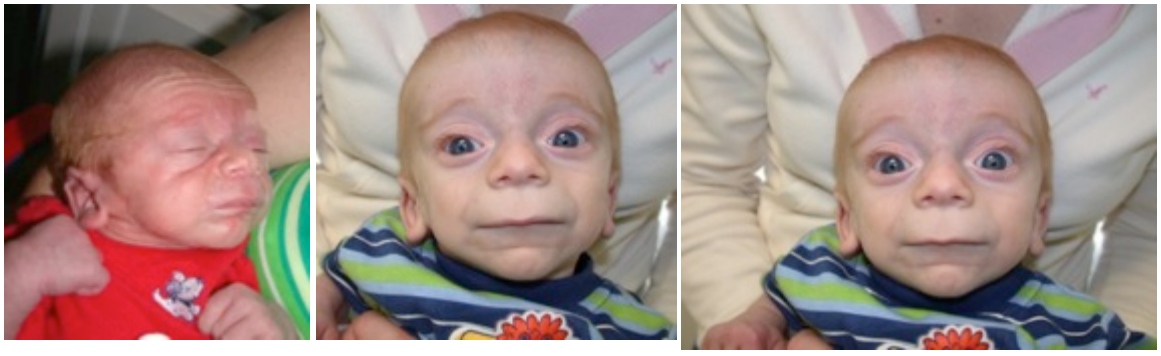

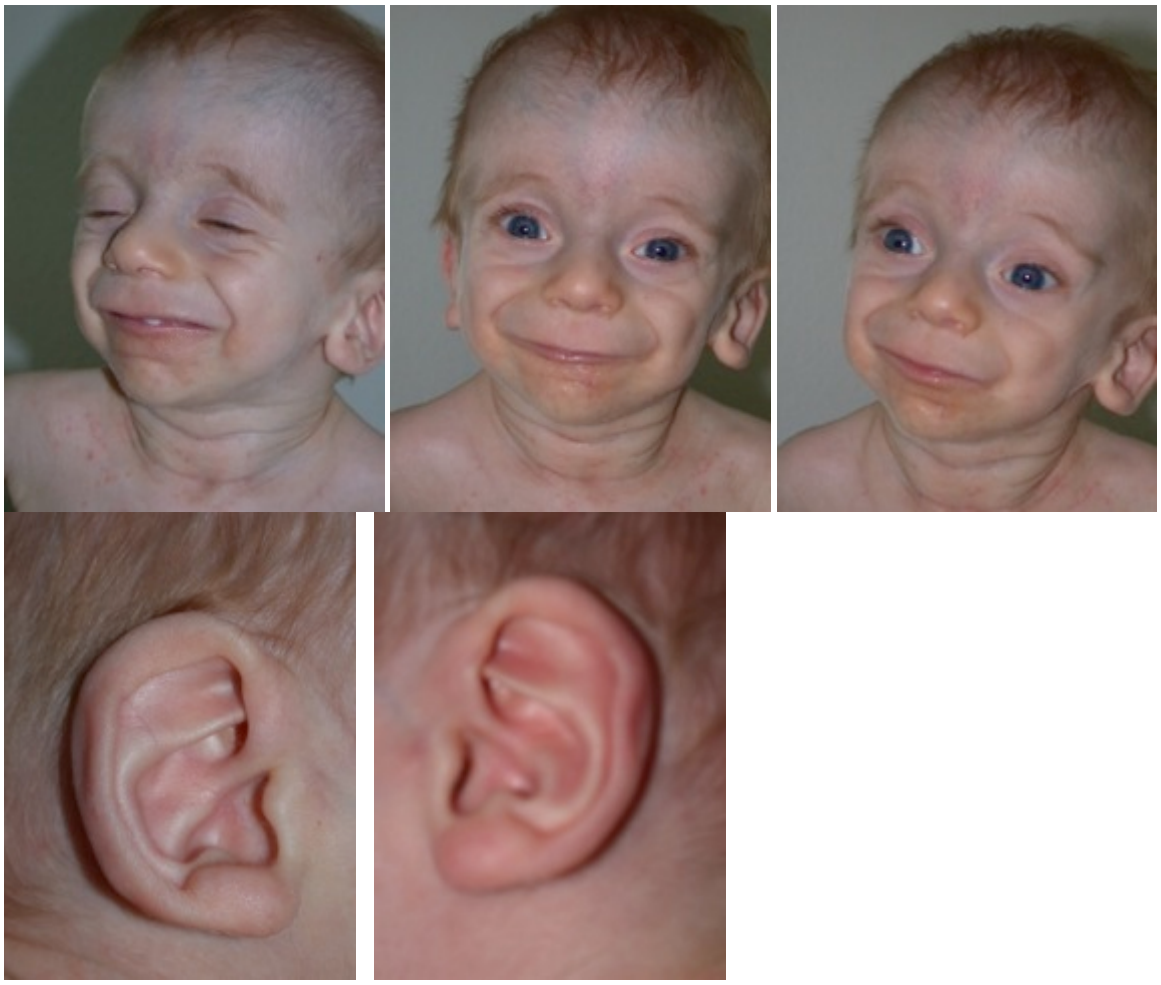

Family 2: Individual III-4