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NSDHL analysis for CHILD syndrome

Clinical Features:

Patients with CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects [OMIM #308050], have a specific lateralization pattern and midline demarcation of an inflammatory epidermal nevus. These skin lesions are usually present at birth and persist throughout life. Alopecia and nail abnormalities are also common. Limb defects (typically hypoplasia or aplasia) occur ipsilateral to the skin defects. Epiphyseal stippling may be noted on radiographs in infancy. Underdevelopment of other organs, including the brain, lungs, heart or kidneys, on the same side as the skin defects may also occur (1-3).

Molecular and Biochemical Genetics:

Mutations of the *NSDHL* [OMIM #300275] gene that codes for a NADH steroid dehydrogenase-like protein (3β-hydroxysteroid dehydrogenase) have been identified in patients with CHILD syndrome (1). This protein functions in the cholesterol biosynthetic pathway and mutations are thought to result in a loss of function. The *NSDHL* gene has 7 coding exons, and over 20 mutations have been identified. Intragenic deletions of one or more exons of the *NSDHL* gene have been reported in a small percentage of patients (2, 4). No clear genotype-phenotype correlations have been reported, most likely due to random X-inactivation. The *NSDHL* gene is the human homolog of *bare patches* (Bpa) and *striated* (Str) in mice that show an X-linked dominant male-lethal phenotype (5). Bornholdt, et al [2005] found mutations in the *NSDHL* gene in 14/14 patients with a clinical and histopathological diagnosis of CHILD syndrome (2).

Patients with CHILD syndrome have increased levels of 4-methyl- and carboxysterols in cultured lymphoblasts. Sterol analysis of plasma and scales from skin lesions is currently used for diagnosis and is available at the Clinical Mass Spectrometry Laboratory at Kennedy Krieger Institute. This test may also distinguish CHILD syndrome from CDPX2 (X-linked dominant chondrodysplasia punctata), a phenotypically similar condition caused by mutations in the *EBP* (emopamil binding protein) gene (2).

Inheritance:

CHILD syndrome is an X-linked condition that is thought to be lethal in males. A heterozygous male has been reported with somatic mosaicism (3). Penetrance appears to be 100%, and incidence does not vary between populations. Recurrence risk for affected individuals and carrier mothers is 50%.

Test methods:

We offer mutation analysis of all 7 coding exons and intron/exon boundaries of *NSDHL* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *NSDHL* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory

NSDHL sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 – 6 weeks

NSDHL deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Results:

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. König A, Happle R, Bornholdt D et al. Mutations in the NSDHL gene, encoding a 3beta-hydroxysteroid dehydrogenase, cause CHILD syndrome. Am J Med Genet 2000: 90: 339-346.
2. Bornholdt D, König A, Happle R et al. Mutational spectrum of NSDHL in CHILD syndrome. J Med Genet 2005: 42: e17.
3. Herman GE. Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. Hum Mol Genet 2003: 12 Spec No 1: R75-88.
4. Kim CA, Konig A, Bertola DR et al. CHILD syndrome caused by a deletion of exons 6-8 of the NSDHL gene. Dermatology 2005: 211: 155-158.
5. Liu XY, Dangel AW, Kelley RI et al. The gene mutated in bare patches and striated mice encodes a novel 3beta-hydroxysteroid dehydrogenase. Nat Genet 1999: 22: 182-187.