



## CHILD syndrome: Mutation Analysis of *NSDHL*

### 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 (3 $\beta$ -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.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

### *NSDHL* mutation analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81404 81405
Turn-around time:	4 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.

*For more information about our testing options, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu) or contact us at 773-834-0555.*

**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, König 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.

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