Smith-Lemli-Opitz Syndrome (*DHCR7*) Sequencing

Indications for Ordering

- Confirm a clinical or biochemical diagnosis of Smith-Lemli-Opitz syndrome(SLOS)
- Carrier screening for SLOS

Test Description

Polymerase chain reaction and Sanger sequencing of *DHCR7* gene

Tests to Consider

Typical testing strategy

Biochemical testing

- 7-dehydrocholesterol (7-DHC) in serum
  - First-tier diagnostic test for individuals suspected to have SLOS
  - Not appropriate for carrier screening
- 7-DHC in amniotic fluid or chorionic villi
  - Recommended initial test when fetus is suspected to have SLOS

Molecular genetic testing

- *DHCR7* gene analysis
  - Confirm suspected diagnosis of SLOS in individuals with equivocal biochemical results
  - Carrier screening for SLOS

Primary tests

Smith-Lemli-Opitz Syndrome (*DHCR7*) Sequencing 2011457

- Diagnostic confirmation or carrier screening for SLOS

Smith-Lemli-Opitz Syndrome (*DHCR7*) Sequencing, Fetal 2011704

- Diagnostic fetal testing for pregnancies suspected to be affected with SLOS

Related tests

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Familial Mutation, Targeted Sequencing, Fetal 2001980

- Fetal test to detect a previously characterized variant in a family member

Disease Overview

Incidence

- 1/10,000-60,000 live births
- Carrier frequency ~1/30-100, depending on ethnicity

Age of onset – prenatal or neonatal

Symptoms

- Characteristic craniofacial features
  - Microcephaly
  - Ptosis, anteverted nares, retrognathia, low-set and posteriorly rotated ears
  - Cleft palate, prominent alveolar ridges
- Cognitive disabilities
  - Autistic behaviors
  - Developmental delay
  - Intellectual disability may be mild to severe
- Genitourinary anomalies
  - Ambiguous genitalia (under-masculinization of male genitalia)
  - Hypospadias and/or cryptorchidism in males
- Growth deficiency
  - Failure to thrive
  - Prenatal/postnatal growth retardation
  - Short stature
- Skeletal findings
  - Postaxial polydactyly
  - 2-3 syndactyly of the toes (minimal to Y-shaped)
- Other features
  - Cardiac defects
  - Congenital cataracts
  - Feeding difficulties
  - Hypotonia
  - Photosensitivity
  - Sensorineural hearing loss

Diagnostic issues

- Typically elevated serum 7-DHC and low or low-normal serum cholesterol due to decreased enzymatic activity of 7-DHC reductase
  - ~10% of affected individuals have normal cholesterol
- Serum 7-DHC level is not sufficient to determine carrier status
  - Reference ranges for carriers and noncarriers overlap
  - Biochemical analysis of fibroblasts can reliably detect carriers
- Psychotropic medications may mildly elevate serum 7-DHC
  - Potential for false-positive serum 7-DHC result

Screening/detection

Maternal serum screening, prenatally

- Low estriol levels (<0.5 multiple of the median [MoM]) in pregnant woman may indicate increased risk for SLOS in fetus

Genetics

Gene – *DHCR7*

Inheritance – autosomal recessive

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 96%
- Analytical sensitivity/specificity – >99%

Results

- Positive
  - Two pathogenic *DHCR7* variants detected
    - If variants occur on opposite chromosomes, consistent with a diagnosis of SLOS
  - One pathogenic *DHCR7* variant detected
    - Individual is at least a carrier of SLOS
    - May be affected with SLOS if an undetected variant is present on the opposite chromosome
- Negative
  - No pathogenic *DHCR7* variants detected
    - Significantly reduces likelihood the individual is affected with or a carrier of SLOS
- Inconclusive
  - Variants of uncertain clinical significance may be identified

Limitations

- Not detected
  - Large deletions/duplications
  - Variants in noncoding exons 1 and 2, promoter, or deep intronic mutations
- Diagnostic errors can occur due to rare sequence variations

References

- Nowaczyk MJM. Smith-Lemli-Opitz Syndrome. 1998 Nov 13 [Updated 2013 Jun 20]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1143/)
- Waterham HR, Hennekam RC. Mutational spectrum of Smith-Lemli-Opitz syndrome. Am J Med Genet Part C Semin Med Genet. 2012;160C:263-284
- Witsch-Baumgartner, Fitzky BU, et al. Mutational spectrum in the D7-sterol reductase gene and genotype-phenotype correlation in 84 patients with Smith-Lemli-Opitz syndrome. Am J Hum Genet. 2000;66:402-412