genzyme

SMN1 Copy Number Analysis

Patient Name: Donor 8538
DOB: [redacted] Age: 30 yrs
SSN #: Gender: Male

803037 / 803038
Seattle Sperm Bank
4915 25th Avenue East
Suite 204W
Seattle, WA 98105
USA

Genzyme Specimen #:61647335-17
Case #: 61533368 Patient ID #: 61362650
Date Collected: 09/02/2010 Date Received: 09/03/2010

Referring Physician: Jeffrey Olliffe
Genetic Counselor:

Client Lab ID #:
Hospital ID #:
Specimen ID #:
Specimen(s) Received: 2 - Yellow (ACD) 10 ml round bottom tube(s)

Specimen Type: Peripheral Blood

Clinical Data: Carrier Test/Gamete donor

Ethnicity: Asian

RESULTS: SMN1 copy number: 2 (Reduced Carrier Risk)

INTERPRETATION:

This individual has an SMN1 copy number of two. This result reduces but does not eliminate the risk to be a carrier of SMA. Ethnic specific risk reductions based on a negative family history and an SMN1 copy number of two are provided in the Comments section of this report.

COMMENT:

Spinal muscular atrophy (SMA) is an autosomal recessive disease of variable age of onset and severity caused by mutations (most often deletions or gene conversions) in the survival motor neuron (SMN1) gene. Molecular testing assesses the number of copies of the SMN1 gene. Individuals with one copy of the SMN1 gene are predicted to be carriers of SMA. Individuals with two or more copies have a reduced risk to be carriers. (Affected individuals have 0 copies of the SMN1 gene.)

This copy number analysis cannot detect individuals who are carriers of SMA as a result of either 2 (or very rarely 3) copies of the SMN1 gene on one chromosome and the absence of the SMN1 gene on the other chromosome or small intragenic mutations within the SMN1 gene. This analysis also will not detect germline mosaicism or mutations in genes other than SMN1. Additionally, de novo mutations have been reported in approximately 2% of SMA patients.

Carrier Frequency and Risk Reductions for Individuals with No Family History of SMA				
Ethnicity	**Detection Rate[1]**	**A priori Carrier Risk[1]**	**Reduced Carrier Risk for 2 copy result**	**Reduced Carrier Risk for 3 copy result**
Caucasian	94.9%	1:35	1:632	1:3,500
Ashkenazi Jewish	90.2%	1:41	1:350	1:4,000
Asian	92.6%	1:53	1:628	1:5,000
Hispanic	90.6%	1:117	1:1061	1:11,000
African American	71.1%	1:66	1:121	1:3,000
Mixed Ethnicities	For counseling purposes, consider using the ethnic background with the most conservative risk estimates.			

METHOD/LIMITATIONS:
Specimen DNA is isolated and amplified by real-time polymerase chain reaction (PCR) for exon 7 of the SMN1 gene and two reference genes. A mathematical algorithm is used to calculate the number of copies of SMN1. Sequencing of the primer and probe binding sites for the SMN1 real-time PCR reaction is performed on all fetal samples, and on samples from individuals with 1 copy of SMN1 on carrier testing, to rule out the presence of sequence variants which could interfere with analysis and interpretation. False positive or negative results may occur for reasons that include genetic variants, blood transfusions, bone marrow transplantation, erroneous representation of family relationships or contamination of a fetal sample with maternal cells.

REFERENCES:
1. Carrier frequency and detection rate are calculated based on analysis of allele frequencies among > 1000 individuals from each ethnic group noted (Genzyme Genetics, data submitted for publication). 2. Online review of SMA: http://www.genereviews.org/profiles/sma

The test was developed and its performance characteristics have been determined by Genzyme. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing. This test must be used in conjunction with clinical assessment, when available.

Electronically Signed by: Narasimhan Nagan, Ph.D., FACMG, on 09/13/2010

Reported by: JC/alw

CEDARS-SINAI MEDICAL CENTER
Department of Pathology and Laboratory Medicine
8700 Beverly Blvd., Los Angeles CA 90048 Tel: (310) 423-5431 Fax: (310) 423-0122
Laboratory Director: Mahul B. Amin, M.D. CLIA # 05D0541033

Patient: UNK, NONORCB 8538 **Accession Number: H-09-09082**

Hospital No: 200057009
Date of Birth: [redacted]
Age/Sex: 30 M
Location: NORCB

Pathologist: Rena E Falk, M.D.
Assistant:
Date of Procedure: 9/15/2009
Date Received: 9/17/2009

Ordering M.D.:
SUSANNE TIMSHEL
Copies To:

CYTOGENETICS REPORT

DIAGNOSIS: Normal karyotype

Specimen Type: Blood	Special Request: No
Test Request: Chromosome Analysis with Banding	

REFERRING DIAGNOSIS / REASON FOR REQUEST: Sperm donor

REPORT

Verbal Report:

CHROMOSOME ANALYSIS:

CULTURE	Number of Cells Counted & Their Chromosomal Complement						
	<45	45	**46**	47	48	>48	Total
72hr			6				6
96hr			14				14

Number of cells analyzed: 2 **# of karyotypes 3** **20**

KARYOTYPING ANALYSIS & RESULTS: 46,XY

COMMENTS:
Cytogenetic analysis using G-banding at the 500-550 band level of resolution on a blood sample from this patient revealed a 46,XY normal male karyotype.

No consistent numerical or structural abnormality was observed, and there was no demonstrable clinically significant abnormality.

INTERPRETATION: Normal Male Karyotype.

I have personally examined the specimen, interpreted the results, reviewed the report and signed it electronically.
Rena E Falk, M.D. Electronically signed 10/7/2009 2:45:43PM

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Laboratory Director: Mahul B. Amin, M.D. CLIA # 05D0541033

Patient: UNK, NONORCB 8538 **Accession Number: H-09-09094**

Hospital No: 200057009
Date of Birth: [redacted]
Age/Sex: 30 M
Location: NORCB
Outreach CPN: 8538

Pathologist: Jean Lopategui, M.D.
Assistant:
Date of Procedure: 9/15/2009
Date Received: 9/16/2009

Ordering M.D.:
SUSANNE TIMSHEL
Copies To:

MOLECULAR PATHOLOGY REPORT

DIAGNOSIS:

CF Carrier Screen Negative Report — PCR-Invader

Cystic Fibrosis Carrier Screen with no Known Family History

RESULT:
NEGATIVE for the mutations analyzed
Revised carrier risk for different ethnic groups is referenced in table below (see comment)

Source: Blood

Indication: Carrier screen. No provided ethnicity. No known family history of cystic fibrosis (CF)

Comment

A negative test result in an asymptomatic patient greatly decreases the risk of being a carrier but ***DOES NOT RULE OUT CF CARRIER*** status. This patient may have rare or private mutations not detected by this panel. The revised carrier risk (risk of being a carrier after a negative test result using this panel) for different ethnic groups with no known family history is referenced in the table below. If further information on ethnicity and family history of CF can be obtained in this patient, please provide them to further define the revised carrier risk. The risk for this patient to have a child with CF is greatly reduced but also depends on the carrier status of the partner.

Clinical Utility

A screening panel of 34 mutations associated with cystic fibrosis is used. It includes the 23 mutations recommended by the American College of Medical Genetics and the American College of Obstetricians and Gynecologists characterized by a frequency > 0.1 % in a pan-ethnic population. It also includes 6 other mutations with a frequency > 0.1 % in a pan-ethnic population and 5 ethnic-specific mutations available by Invader with a frequency > 0.1% in the Hispanic, African American and Asian populations. An accurate assessment of the revised carrier risk (also called residual carrier risk) after a negative test result for the mutations analyzed by this panel requires information on ethnic origin, prior carrier risk, mutation detection rate of this panel, and family history.

PATIENT: UNK, NONORCB 8538 **ACCESSION #:** H-09-09094

Ethnic Origin	*Prior Carrier Risk*	*Mutation Detection Rate*	*Revised Carrier Risk After Negative Testing*
US Caucasian origin unspecified	1/29	80%	1/140
Northern European Caucasian*	1/29	90%	1/280
Southern European Caucasian*	1/29	72%	1/100
Ashkenazi Jewish	1/29	97%	1/934
Hispanic American	1/46	57%	1/105
African American	1/65	69%	1/207
Asian American	1/90	25%	1/120

* Northern Europe includes the Alps and southern Europe is south of the Alps

Method

DNA is extracted by Qiagen silica-gel column. The assay is performed on the FDA-cleared Invader® platform with specific oligonucleotides to detect the 23 ACMG recommended mutations associated with cystic fibrosis. The additional 11 mutations described above, 6 pan-ethnic (Q493X, S549N, 3905insT, E60X, Y1092X, 2183delAA>G) and 5 ethnic specific (V520F, R347H, D1270N, D1152H, 3876delA) are run on the same platform. Testing for intron 8 5T polymorphism is performed only when the R117H mutation is detected.

References

1. Lebo V and Grody W., Testing and reporting ACMG cystic fibrosis mutation panel results, Genetic Testing 11: 11, 2007
2. Langfelder-Schwind E et al, Cystic fibrosis prenatal screening in genetic counseling practice: Recommendations of the National Society of Genetic Counselors, Journal of Genetic Counseling 14:1, 2005
3. Watson M et al, Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel, Genetics in Medicine, 6: 387, 2004
4. Richards CS et al, Standards and guidelines for CFTR mutation testing, Genetics in Medicine 4: 379, 2002

JL/tvt
09/18/09

I have personally examined the specimen, interpreted the results, reviewed the report and signed it electronically.
Jean Lopategui, M.D. Electronically signed 9/18/2009 5:48:57PM