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Date of Report: August 3, 2001
Date of Service: July 6, 2001

TO: David Lynch, M.D. / Jennifer Farmer, M.S.
RE: Stephen Duncan-Smith

Date of Birth: 9/3/56

Test Requested: Level 1 Screening of the Notch3 Gene for CADASIL Mutation

RESULT:

Stephen Duncan-Smith is heterozygous for a C to T base change at nucleotide 505 of the Notch 3 gene that changes a codon for arginine (CGC) to one for cysteine (TGC) at amino acid position 169. This mutation has been reported previously in patients with CADASIL.

INTERPRETATION:

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is due to characteristic missense mutations in the Notch3 gene. These mutations typically result in the gain or loss of a cysteine residue in the epidermal growth factor (EGF)-like domains in the extracellular region of the protein. The analysis performed here is expected to detect 93% of mutations in individuals with skin biopsy proven CADASIL. The mutation identified in this patient is consistent with the known pathobiochemistry of the disease.

Method:

Analysis of heteroduplexes of amplified genomic DNA from specific exons and intron-exon boundaries of the Notch3 gene by conformation sensitive gel electrophoresis (CSGE) followed by direct DNA sequence analysis of aberrantly migrating PCR products. Nucleotides are numbered according to the published coding sequence starting with the first base of the initiator methionine. Level 1 analysis: Exons 3, 4, 11, 18, & 19. Level 2 analysis: Exons 2, 5, 8, 14, & 22-23.

References: Ganguly et al, *Proc. Natl. Acad. Sci. USA* 90: 10325-10329, 1993.
Joutel et al. *Lancet* 350: 1511-1515, 1997.
Lesnik Oberstein et al. *Neurology* 52: 1913-1915, 1999.

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ABSTRACT <http://jnnp.bmjournals.com/cgi/content/full/74/6/790>

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by point mutations in the Notch3 gene. Presenilins are proteins involved in the cleaving of both Notch and the amyloid precursor protein (APP). In cases of early onset Alzheimer's disease mutations of the presenilin genes (PSEN 1 and PSEN 2) and APP can be found. A 64 year old patient with CADASIL (**R169C-mutation**) is reported, who, in addition to subcortical infarcts and granular osmiophilic deposits, had numerous senile plaques and neurofibrillary tangles on pathological examination. Mutations in the APP, PSEN1, and PSEN2 genes were not identified. Neuropathological findings of Alzheimer's disease may be found in CADASIL patients.

CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUCOENCEPHALOPATHY (CADASIL) http://www.esc-bologna.org/bologna.asp/bo_po_34.asp

Genetic studies of the notch 3 gene detected a heterozygous **Arg169Cys** (CGC/TGC) mutation in the protein coding sequence of exon 4, confirming the diagnosis of CADASIL.