Senior-Loken Syndrome (SLS) Panel

Disorder also known as: Senior-Løken syndrome, Loken-Senior syndrome, renal dysplasia and retinal aplasia, renal-retinal syndrome

Panel Gene List: CEP290 (NPHP6), INVS (NPHP2), IQCB1 (NPHP5), NPHP1, NPHP3, TRAF3IP1

Clinical Features:
Senior-Loken syndrome (SLS) is a rare early-onset disorder with a prevalence of 1:1,000,000.[1] Patients present with nephronophthisis (NPHP) and Leber congenital amaurosis (LCA), usually progressing to blindess and end-stage renal disease (ESRD) within the first two decades of life.[2] NPHP is characterized by cystic kidney disease, reduced renal concentrating ability, and chronic inflammation of the renal tubules. Many patients experience frequent urination during the day and night, leading to excessive thirst.[1,3] LCA is typically characterized by moderate to severe visual imparement starting at infancy.

SLS is part of a larger group of nephronothisis-related ciliopathies (NPHP-RC) that share a wide variety of phenotypic overlap due to multi-organ involvment. This multi-organ involvement is due to the fact that SLS is caused by defects in genes that code for primary cilia proteins that are involved in the development and function of multiple cell types, including renal and retinal cells.[4] Within this group, SLS is most commonly characterized by retinal degeneration.[5,6] Other NPHP-RC include Joubert syndrome (JS), Meckel–Gruber syndrome (MKS), LCA, Bardet-Biedl, Jeune syndrome and related skeletal disorders, among others.

Inheritance Pattern/Genetics:
Autosomal Recessive

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Of note, the CEP290 intronic c.2991+1655 A>G (IVS26+1655) pathogenic variant is also captured by our methodology. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy

number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined SLS or a family history of disease. Specific information about the sensitivity for each gene in selected populations is summarized in the table below.

Gene	Protein	Inheritance	Disease Phenotype	Sensitivity
CEP290 (NPHP6)	Centrosomal protein 290KD	AR	SLS 6 / JS 5 / LCA 10 / MKS 4	6/67 of individuals with SLS[5,7] ~2-6% of NPHP-RC[5,6]
INVS (NPHP2)	Inversin	AR	NPHP 2	Rare in SLS[5] 1-2% of NPHP[6,8,9] ~1-4% of NPHP-RC[5,6]
IQCB1 (NPHP5)	IQ motif containing B1	AR	SLS 5	35/67 individuals with SLS[5,7] ~2-7% of NPHP-RC[5,6,7]
NPHP1	Nephrocystin 1	AR	JS 4 / NPHP 1 / SLS 1	4/17 individuals with SLS[5] ~15-20% of NPHP-RC[5,7]
NPHP3	Nephrocystin 3	AR	MKS 7 / NPHP 3 / RHPD 1	Rare in SLS[5,7] ~2-3% of NPHP-RC[5,6]

TRAF3IP1	TRAF3 interacting protein 1	AR	SLS 9	<1% of NPHP-RC[10]

Abbreviations: AR – Autosomal Recesive ; JS – Joubert syndrome ; LCA – Leber congenital amaurosis ; MKS – Meckel-Gruber syndrome ; NPHP – Nephronophthisis ; NPHP-RC – Nephronophthisis-Related Ciliopathies ; RHPD – Renal-hepatic-pancreatic dysplasia ; SLS – Senior-Loken syndrome

References:

1. Tsang S.H., Aycinena A.R.P., Sharma T. (2018) Adv Exp Med Biol. 2018;1085:175-178 (PMID: 30578507)
2. Yu PH, Kuo YR, Altmüller J, Hwang DY. Kaohsiung J Med Sci. 2018;34(10):588-589. (PMID: 30309488)
3. Tong et al. (2013) Nephrology (Carlton) 18 (12):838-42 (PMID: 24674142
4. Kaur A, Dhir SK, Goyal G, Mittal N, Goyal RK. (2016) J Clin Diagn Res. 2016 Nov;10(11):SD03-SD04(PMID: 28050464)
5. Chaki et al. (2011) Kidney Int. 80 (11):1239-45 (PMID: 21866095)
6. Halbritter et al. (2013) Human Genetics 132 (8):865-84 (PMID: 23559409)
7. König et al. (2017) Clin J Am Soc Nephrol 12 (12):1974-1983 (PMID: 29146700)
8. Tory et al. (2009) Kidney International 75 (8):839-47 (PMID: 19177160)
9. Braun et al. (2016) Kidney Int. 89 (2):468-75 (PMID: 26489029)
10. Bizet et al. (2015) Nat Commun 6 :8666 (PMID: 26487268)