

Genetic testing for Senior-Loken syndrome

Andi Abeshi^{1,2}, Alessandra Zulian³, Tommaso Beccari⁴, Munis Dundar⁵, Leonardo Colombo⁶
and Matteo Bertelli^{2,3}

Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for Senior-Loken syndrome (SLSN). SLSN is inherited in an autosomal recessive manner, has a prevalence of one in a million, and is caused by variations in *CEP164*, *CEP290*, *INVS*, *IQCB1*, *NPHP1*, *NPHP3*, *NPHP4*, *SDCCAG8*, *TRAF3IP1* and *WDR19* genes. Clinical diagnosis is based on kidney (urine analysis, abdominal ultrasound, kidney function) and eye assessment (visual acuity test, fundus examination, refraction defects, color testing and electroretinography). The genetic test is useful for confirming diagnosis, and for differential diagnosis, couple risk assessment and access to clinical trials.

¹MAGI Balkans, Tirana, Albania

²MAGI'S Lab, Rovereto, Italy

³MAGI Euregio, Bolzano, Italy

⁴Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy

⁵Department of Medical Genetics, Erciyes University Medical School, Kayseri, Turkey

⁶Department of Ophthalmology, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy

Corresponding author: M. Bertelli
E-mail: info@assomagi.org

Published online: 27 October 2017

doi:10.24190/ISSN2564-615X/2017/S1.31

Senior-Loken syndrome

(other synonyms: Loken-Senior syndrome, renal dysplasia and retinal aplasia, renal-retinal syndrome) (ghr.nlm.nih.gov)

General information about the disease

Senior-Loken Syndrome (SLSN) is a rare genetic disorder with oculo-renal involvement and nephronophthisis (NPHP, OMIM: 256100) and Leber congenital amaurosis (LCA, OMIM: 204000) as main features (1). It is characterized by congenital or childhood onset with symptoms and signs of NPHP and LCA. NPHP findings include polyuria, anemia, polydipsia and enuresis. Progression of the disease can lead to acute or chronic kidney failure and eventually to end-stage kidney disease.

Ocular findings include severe visual loss at birth or in early childhood, photophobia, hyperopia and nystagmus. Other systemic findings such as obesity, liver fibrosis (2) and neurological disorders may also be present.

The prevalence of SLSN is reported to be one per million (retrieved from Orphanet).

Diagnosis of SLSN is based on clinical kidney and ocular findings (urine analysis, abdominal ultrasound, kidney function, visual acuity, fundus examination, refraction defects, color testing and electroretinography). It is confirmed by detection of pathogenic variants in known causative genes.

Differential diagnosis should consider other disorders associated with eye and kidney involvement such as Joubert syndrome with oculorenal defect, Bardet-Biedl syndrome and Alström syndrome.

SLSN is transmitted in an autosomal recessive manner and is caused by variations in the following genes: *CEP164* (OMIM gene: 614848; OMIM disease: 614845), *CEP290* (OMIM gene: 610142; OMIM disease: 610189), *INVS* (OMIM gene: 243305; OMIM disease: 602088), *IQCB1* (OMIM gene: 609237; OMIM disease: 609254), *NPHP1* (OMIM gene: 607100; OMIM disease: 266900), *NPHP3* (OMIM gene: 608002; OMIM disease:

604387), *NPHP4* (OMIM gene: 607215; OMIM disease: 606996), *SDCCAG8* (OMIM gene: 613524; OMIM disease: 613615), *TRAF3IP1* (OMIM gene: 607380; OMIM disease: 616629) and *WDR19* (OMIM gene: 608151; OMIM disease: 616307).

Pathogenic variants may include small intragenic deletions/insertions, as well as splice-site, missense, nonsense and deep intronic variants; exon or whole-gene duplications/deletions have also been reported for *CEP290*, *NPHP1*, *NPHP4*, and *SDCCAG8* genes.

Aims of the test

- To determine the gene defect responsible for the pathology;
- To confirm clinical diagnosis of the disease;
- To determine carrier status for the disease.

Test characteristics

Experts centers/Published guidelines

The test is listed in the Orphanet database and is offered by 13 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 13 accredited medical genetic laboratories in the US.

The guidelines for clinical use of the test are described in “Genetics home reference” (ghr.nlm.nih.gov).

Test strategy

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in *CEP164*, *CEP290*, *INVS*, *IQCB1*, *NPHP1*, *NPHP3*, *NPHP4*, *SDCCAG8*, *TRAF3IP1* and *WDR19* genes. Potentially causative variants and regions with low coverage are Sanger-sequenced. MLPA is used for detection of duplications/deletions in *CEP290* and *NPHP1* genes. Sanger sequencing is also used for family segregation studies

The test identifies variations in known causative genes in patients suspected to have SLSN. To perform molecular diagnosis, a single sample of biological material is normally sufficient. This may be 1 ml blood in a sterile tube with 0.5 ml K3EDTA or 1 ml saliva in a sterile tube with 0.5 ml ethanol 95%. Sampling rarely has to be repeated. Gene-disease associations and interpretation of genetic variants are rapidly developing fields. It is therefore possible that the genes mentioned in this note may change as new scientific data is acquired. It is also possible that genetic variants today defined as of “unknown or uncertain significance” may acquire clinical importance.

Genetic test results

Positive

Identification of pathogenic variants in *CEP164*, *CEP290*, *INVS*, *IQCB1*, *NPHP1*, *NPHP3*, *NPHP4*, *SDCCAG8*, *TRAF3IP1* or *WDR19* genes confirms the clinical diagnosis and is an indication for family studies.

A pathogenic variant is known to be causative for a given genetic disorder based on previous reports or predicted to be

causative based on the loss of protein function or expected significant damage to protein or protein/protein interactions. In this way it is possible to obtain a molecular diagnosis in new/other subjects, establish the risk of recurrence in family members and plan preventive and/or therapeutic measures.

Inconclusive

Detection of a variant of unknown or uncertain significance: a new variation and/or without any evident pathogenic significance or with insufficient or significant conflicting evidence to indicate it is likely benign or likely pathogenic for a given genetic disorder. In these cases, it is advisable to extend testing to the patient's relatives in order to assess variant segregation and clarify its contribution. In some cases it could be necessary to perform further examinations/tests or to do a clinical reassessment of pathological signs.

Unexpected

Unexpected results may come out from the test, for example information regarding consanguinity; absence of family correlation or the possibility of developing genetically based diseases.

Negative

The absence of variations in the genomic regions investigated does not exclude a clinical diagnosis but suggests the possibility of:

- alterations that cannot be identified by sequencing, such as large rearrangements that cause loss (deletion) or gain (duplication) of extended gene fragments;
- sequence variations in gene regions not investigated by this test, such as regulatory regions (5' and 3' UTR) and deep intronic regions;
- variations in other genes not investigated by the present test.

Risk for progeny

Autosomal recessive transmission needs that both healthy carrier parents transmit their disease variant to his/her children. In this case, the probability of having an affected boy or girl is therefore 25%.

Limits of the test

The test is limited by current scientific knowledge regarding the genes and disease.

Analytical sensitivity (proportion of positive tests when the genotype is truly present) and analytical specificity (proportion of negative tests when the genotype is not present)

NGS: Analytical sensitivity: >99% (with a minimum coverage of 10X); Analytical specificity: 99.99%.

SANGER: Analytical sensitivity: >99.99%; Analytical specificity: 99.99%.

MLPA: Analytical sensitivity: >99.99%; Analytical specificity: 99.99%.

Clinical sensitivity (proportion of positive tests if the disease is present) and clinical specificity (proportion of negative tests if the disease is not present)

Clinical sensitivity: is estimated at approximately 20-30% [Author's laboratory data] (3).

Clinical specificity: is estimated at approximately 99.99% [Author's laboratory data] (3).

Prescription appropriateness

The genetic test is appropriate when:

- a) the patient meets the diagnostic criteria for the disease;
- b) the genetic test has diagnostic sensitivity greater than or equal to other published tests.

Clinical utility

Clinical management	Utility
Confirmation of clinical diagnosis	yes
Differential diagnosis	yes
Access to clinical trial (4)	yes
Couple risk assessment	yes

References

1. Loken AC, Hanssen O, Halvorsen S, Jolster NJ. Hereditary renal dysplasia and blindness. *Acta Paediatr.* 1961 Mar; 50:177-84. PubMed PMID: 13763238
2. Delaney V, Mullaney J, Bourke E. Juvenile nephronophthisis, congenital hepatic fibrosis and retinal hypoplasia in twins. *Q J Med.* 1978 Jul; 47(187):281-90. PubMed PMID: 568809
3. Chen B, Gagnon M, Shahangian S, Anderson NL, Howerton DA, Boone JD. Good laboratory practices for molecular genetic testing for heritable diseases and conditions. *MMWR Recomm Rep.* 2009 Jun 12; 58(RR-6):1-37. PubMed PMID: 19521335.
4. Stone EM, Aldave AJ, Drack AV, Maccumber MW, Sheffield VC, Traboulsi E, Weleber RG. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. *Ophthalmology.* 2012 Nov; 119(11):2408-10. PubMed PMID: 22944025. Epub 2012/09/01.