DNA ligase deficiency IV

GENERAL INFORMATION

Description:

Defects in LIG44 are the cause of LIG44 syndrome. This disease is characterized by immunodeficiency and developmental and growth delay. Patients display unusual facial features, microcephaly, growth and/or developmental delay, pancytopenia, and various skin abnormalities.

Alternative names:

- LIG4
- LIG4 syndrome

Classification:

- DNA breakage associated syndromes and DNA epigenetic modification syndromes
  - DNA ligase deficiency

Inheritance:

Autosomal recessive

OMIM:

- #606593 LIG4 syndrome
- *601837 Ligase IV, DNA, ATP-dependent; LIG4

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for Nijmegen-breakage syndrome

Incidence:

Incidence is not known.

CLINICAL INFORMATION

Description:

The clinical phenotype closely resembled the DNA damage response disorder, Nijmegen breakage syndrome. Patients displayed unusual facial features, microcephaly, growth and/or developmental delay, pancytopenia, and various skin abnormalities. Cell lines from the patients showed pronounced radiosensitivity.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Nijmegen breakage syndrome, ORPHANET
- Nijmegen breakage syndrome, eMedicine

Therapeutic options:

- Nijmegen breakage syndrome, eMedicine

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies
- Molecular and Clinical Studies of Primary Immunodeficiency diseases, ClinicalTrials.gov

GENE INFORMATION

Names:

HUGO name: LIG4
Alias(es): Sealase, DNA joinase, DNA repair enzyme, Ligase IV, DNA, ATP-dependent, Polydeoxyribonucleotide synthase, Polynucleotide ligase, DNA ligase IV , EC 6.5.1.1, Polydeoxyribonucleotide synthase [ATP]

Localization:

Reference sequences:

DNA: X83441 (EMBL) AF479264 (EMBL) , **cDNA:** X58957 (EMBL) , **Protein:** P49917 (SWISSPROT)

Chromosomal Location:

13q22-q34

Maps:

LIG4 (Map View)

Markers:

D13S1452, SGC35475, RH98317

Variations / Mutations:

- LIG4base; Mutation registry for LIG4 syndrome

Other gene-based resources:

Ensembl: ENSG00000174405, GENATLAS: LIG4, GeneCard: LIG4, UniGene: 166091, Entrez Gene: 3981, euGenes: 3981, GDB: 624512, HomoloGene: 1736

PROTEIN INFORMATION

Description:

Protein function:

Efficiently joins single-strand breaks in a double-stranded polydeoxynucleotide in an ATP-dependent reaction. Involved in DNA nonhomologous end joining (NHEJ) required for double-strand break repair and V(D)J recombination. Binds to XCRCC4. The LIG4-XRCC4 complex is responsible for the NHEJ ligation step, and XRCC4 enhances the joining activity of LIG4. Binding of the LIG4-XRCC4 complex to DNA ends is dependent on the assembly of the DNA-dependent protein kinase complex DNA-PK to these DNA ends.

Catalytic activity:

ATP + {deoxyribonucleotide}(n) + {deoxyribonucleotide}(m) = AMP + diphosphate + {deoxyribonucleotide}(n+m)

Subunit:

The LIG4-XRCC4 complex has probably a 1:2 stochiometry. The LIG4-XRCC4 heteromer associates in a DNA-dependent manner with the DNA-dependent protein kinase complex DNA-PK, formed by the KU p70/p86 dimer (g22p1/g22p2) and PRKDC.

Subcellular location:

Nuclear

Tissue specificity:

Testis, thymus, prostate and heart.

Similarity:

Belongs to the ATP-dependent DNA ligase family.

Structures (PDB):

1IK9 Crystal Structure Of A Xrcc4-DNA Ligase IV Complex

Domains:

BRCT 1 domain: 587-676

BRCT 2 domain: 741-844

Other features:

Amp binding site: 206

Other related resourses:

PIR: I37079, InterPro: IPR001357; BRCT, InterPro: IPR000977; DNA_ligase, Pfam: PF00533; BRCT, Pfam: PF01068; DNA_ligase, Pfam: PF04679; DNA_ligase_A_C, Pfam: PF04675; DNA_ligase_A_N, SMART: SM00292; BRCT, PROSITE: PS50172; BRCT, PROSITE: PS00697; DNA_LIGASE_A1, PROSITE: PS00333; DNA_LIGASE_A2, PROSITE: PS50160; DNA_LIGASE_A3

Expression pattern for human:

Tissue	Exp. (%)	Clones
juvenile granulosa tumor	18.16	1:2159
thymus	17.92	1:2187
fetal liver	8.83	1:4439
pituitary	6.80	1:5766
corresponding non cancerous liver tissue	5.94	2:13205
glioblastoma	5.54	1:7072
leukopheresis	5.05	1:7769
chondrosarcoma grade II	4.90	1:8000
cochlea	4.55	1:8607
total brain	3.70	1:10594
juvenile granulosa tumor	18.16	1:2159
thymus	17.92	1:2187
fetal liver	8.83	1:4439
pituitary	6.80	1:5766
corresponding non cancerous liver tissue	5.94	2:13205
glioblastoma	5.54	1:7072
leukopheresis	5.05	1:7769
chondrosarcoma gradeII	4.90	1:8000
cochlea	4.55	1:8607
total brain	3.70	1:10594

Animal models:

Mouse:

MGD: ; Lig4

OTHER RESOURCES

Societies:

General:

- International Patient Organization for Primary Immunodeficiencies
- Immune Deficiency Foundation
- European Society for Immunodeficiencies