Pathway of a Rare Disease
Joubert Syndrome

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Introduction - General Information

- Rare hereditary disorder
  - Prevalence: 1 in 80,000-100,000
  - Autosomal recessive inheritance
- >30 genes
- Ciliopathy
  - Primary cilium affected
  - Wnt, SHH
- Molar Tooth Sign
- Motor/intellectual development

Figure 1. Molar tooth sign.

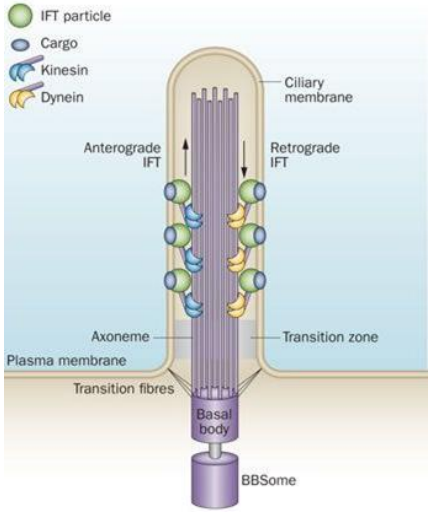


Figure 2. Primary cilium.

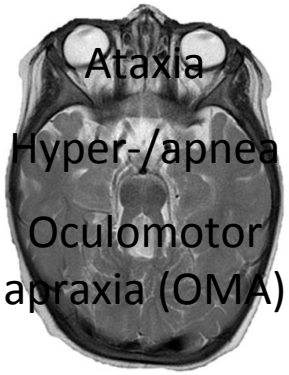
- Brooks BP, Zein WM, Thompson AH, Mokhtarzadeh M, Doherty DA, Parisi M, et al. Joubert Syndrome: Ophthalmological Findings in Correlation with Genotype and Hepatorenal Disease in 99 Patients Prospectively Evaluated at a Single Center. Ophthalmology. 2018;125(12):1937-52.
- Coene KL, Roepman R, Doherty D, Afroze B, Kroes HY, Letteboer SJ, et al. OFD1 is mutated in X-linked Joubert syndrome and interacts with LCA5-encoded lebercilin. Am J Hum Genet. 2009;85(4):465-81.
- Badano JL, Mitsuma N, Beales PL, Katsanis N. The ciliopathies: an emerging class of human genetic disorders. Annu Rev Genomics Hum Genet. 2006;7:125-48.
- Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. Orphanet J Rare Dis. 2010;5:20.

Figure 1. Molar tooth sign (MTS). Case courtesy of Dr Mohammad A. ElBeialy, Radiopaedia.org, rID: 27965. Available from https://radiopaedia.org/articles/molar-tooth-sign-cns-1

Figure 2. Primary cilia in neurodevelopmental disorders. Valente et al., 2013. Available from https://www.nature.com/articles/nrneurol.2013.247

Introduction - Phenotype

Brain

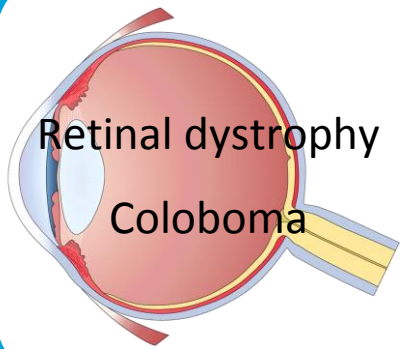


Ataxia

Hyper-/apnea

Oculomotor apraxia (OMA)

Eye

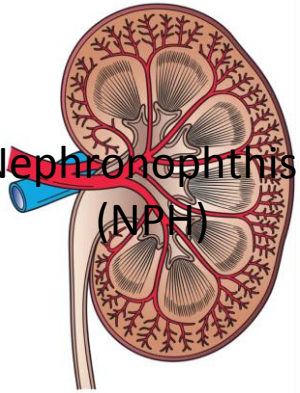


Retinal dystrophy

Coloboma

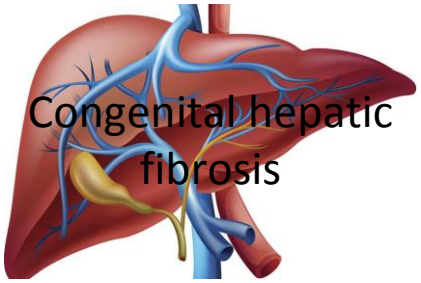
Figure 3. Microscopic image of primary cilium.

Kidney



Nephronophthisis (NPH)

Liver



Congenital hepatic fibrosis

- Brooks BP, Zein WM, Thompson AH, Mokhtarzadeh M, Doherty DA, Parisi M, et al. Joubert Syndrome: Ophthalmological Findings in Correlation with Genotype and Hepatorenal Disease in 99 Patients Prospectively Evaluated at a Single Center. Ophthalmology. 2018;125(12):1937-52.
- Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. Orphanet J Rare Dis. 2010;5:20.

Figure 3. Molar tooth sign (MTS). Case courtesy of Dr Mohammad A. ElBeialy, Radiopaedia.org, rID: 27965. Available from https://radiopaedia.org/articles/molar-tooth-sign-cns-1
Primary cilium. Liem et al., 2012. Available from http://lmcs.cent.uw.edu.pl/research/ciliary-biology/

Aim

Synthesize a visual representation of the pathways underlying Joubert Syndrome pathogenesis.

Methods - Data Collection

PubMed

Google Scholar

- Finding general information

- Overview involved genes
- Facilitation more targeted literature search
- Creation of rough outline functional units + molecular interactions

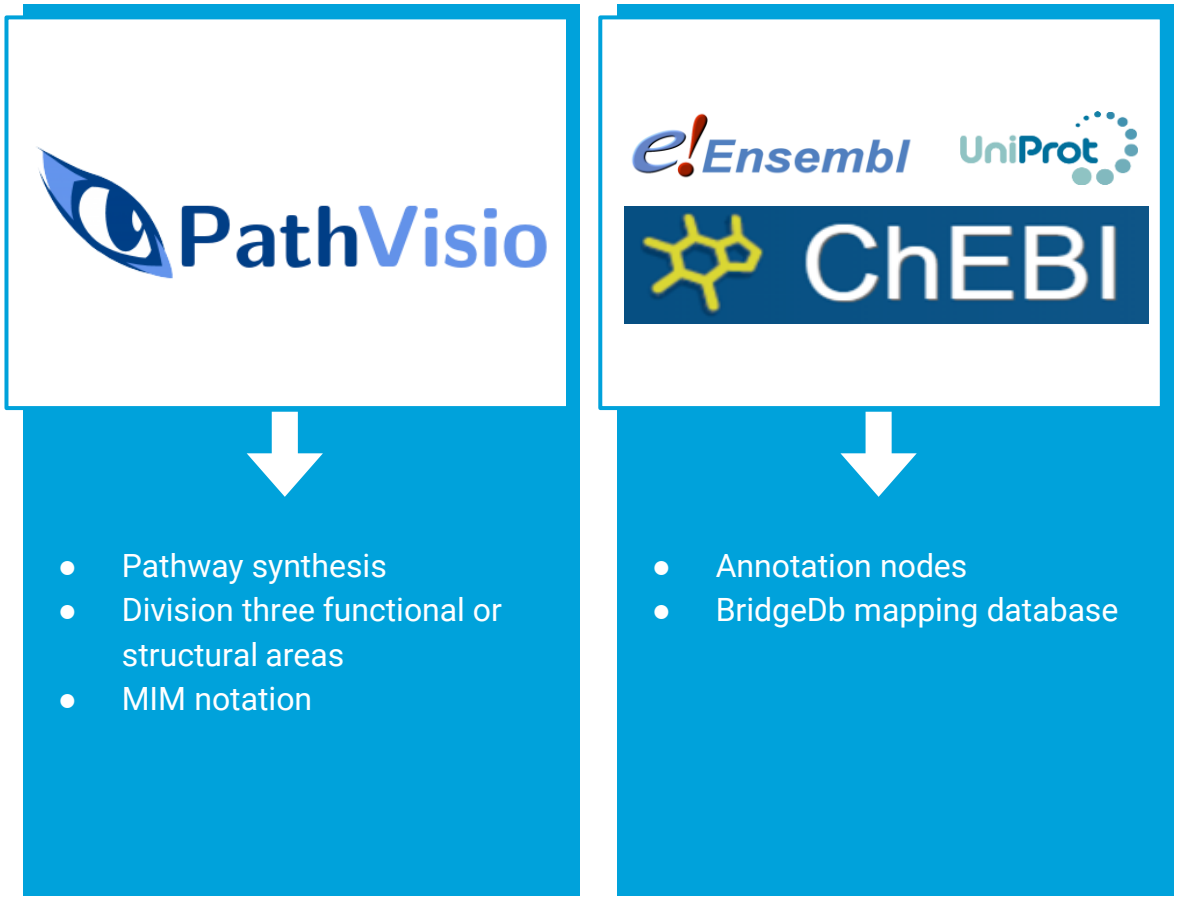
WikiPathways
Pathways for the People

STRING GeneMANIA

- Compile and combine known pathways
- Finding new interactions
- Finding experimental data supporting interactions

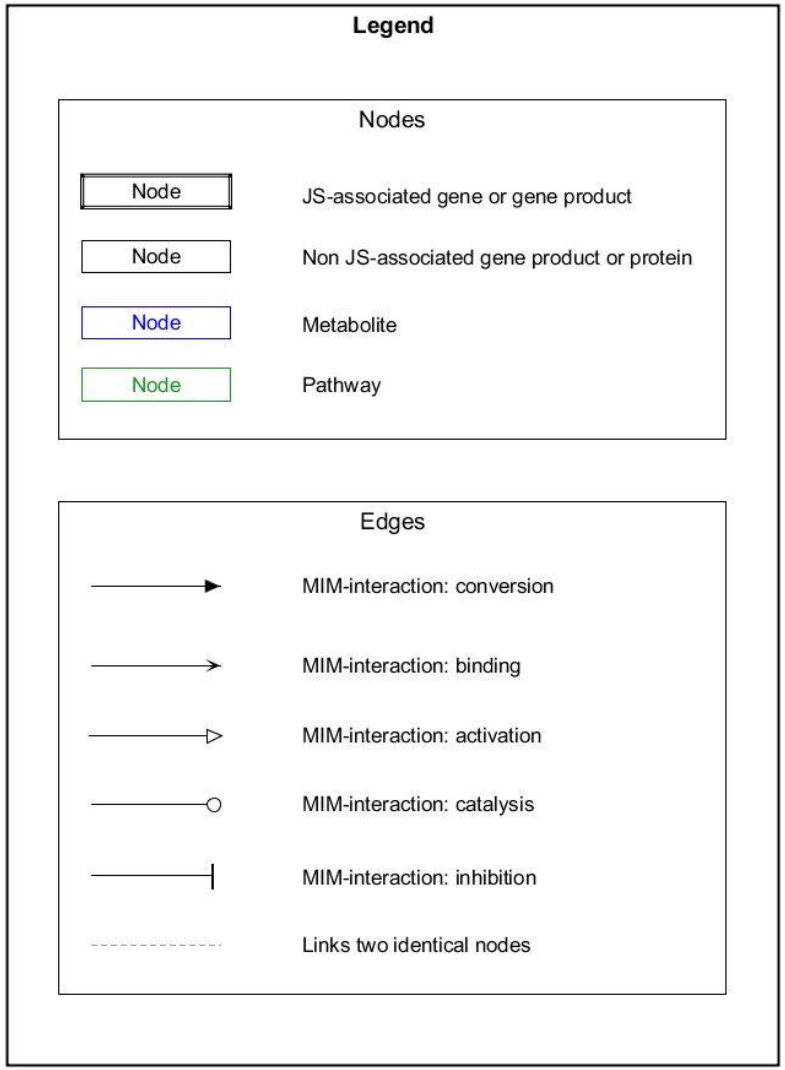
- Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res. 2005;33(Database issue):D514-7.
- Slenter DN, Kutmon M, Hanspers K, Riutta A, Windsor J, Nunes N, et al. WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. Nucleic Acids Res. 2018;46(D1):D661-D7.
- Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M, et al. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. Nucleic Acids Res. 2017;45(D1):D362-D8.
- Warde-Farley D, Donaldson SL, Comes O, Zuberi K, Badrawi R, Chao P, et al. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. Nucleic Acids Res. 2010;38:W214-20.

Methods - Pathway Building

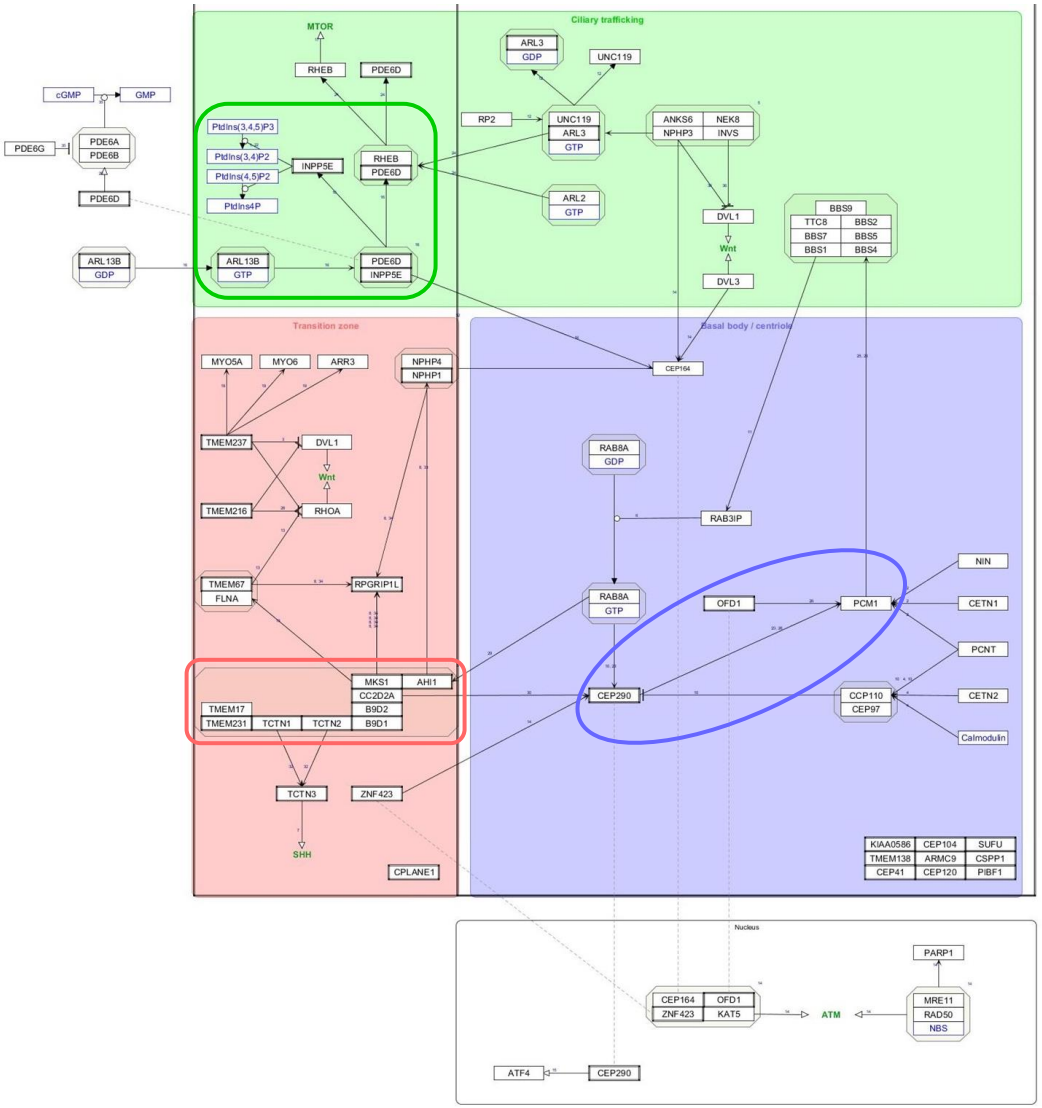


- Kutmon M, van Iersel MP, Bohler A, Kelder T, Nunes N, Pico AR, et al. PathVisio 3: an extendable pathway analysis toolbox. PLoS Comput Biol. 2015;11(2):e1004085.
- Molecular interaction maps of bioregulatory networks: a general rubric for systems biology. Mol Biol Cell. 2006;17(1):1-13.
- Zerbino DR, Achuthan P, Akanni W, Amode MR, Barrell D, Bhai J, et al. Ensembl 2018. Nucleic Acids Res. 2018;46(D1):D754-D61.
- UniProt C. The universal protein resource (UniProt). Nucleic Acids Res. 2008;36:D190-5.
- Hastings J, de Matos P, Dekker A, Ennis M, Harsha B, Kale N, et al. The ChEBI reference database and ontology for biologically relevant chemistry: enhancements for 2013. Nucleic Acids Res. 2013;41:D456-63.
- Van Iersel MP, Pico AR, Kelder T, Gao J, Ho I, Hanspers K, et al. The BridgeDb framework: standardized access to gene, protein and metabolite identifier mapping services. BMC Bioinformatics. 2010;11:5.

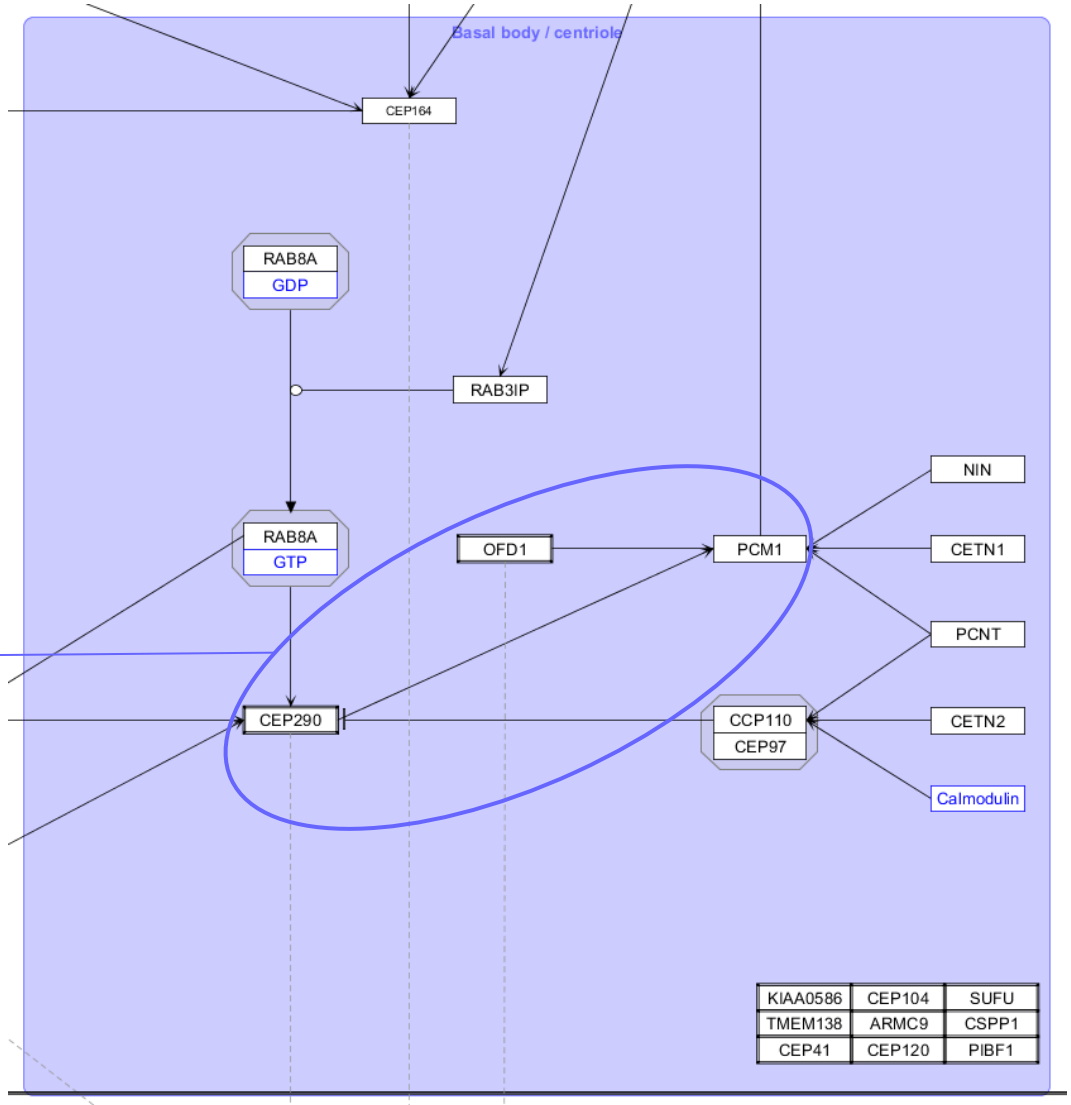
Results - Legend



Results - Overall Pathway

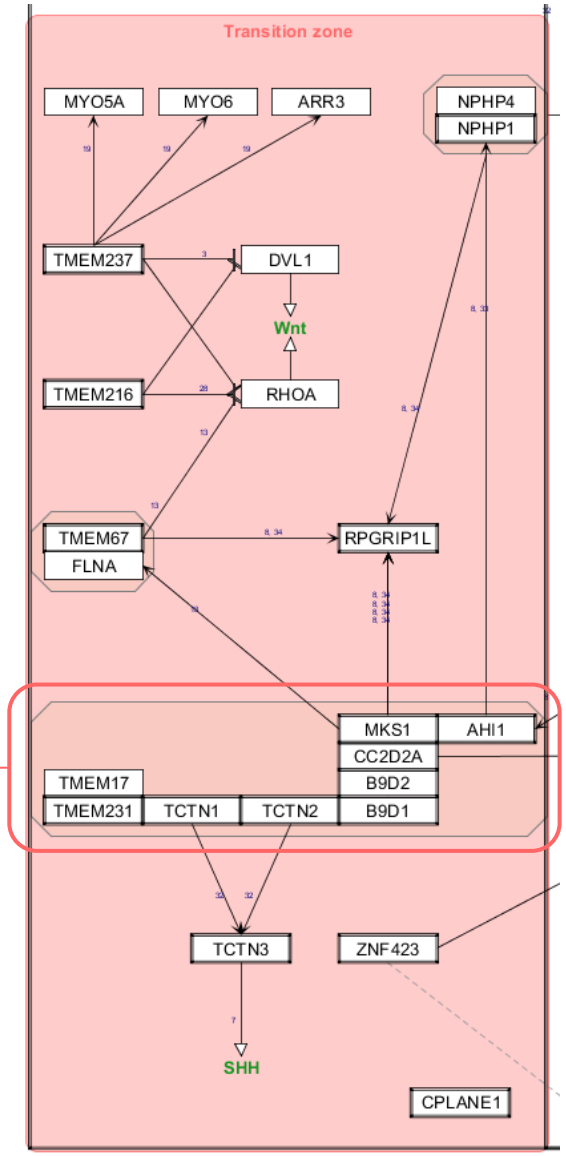


Results - Basal body / Centriole



Centriolar satellite

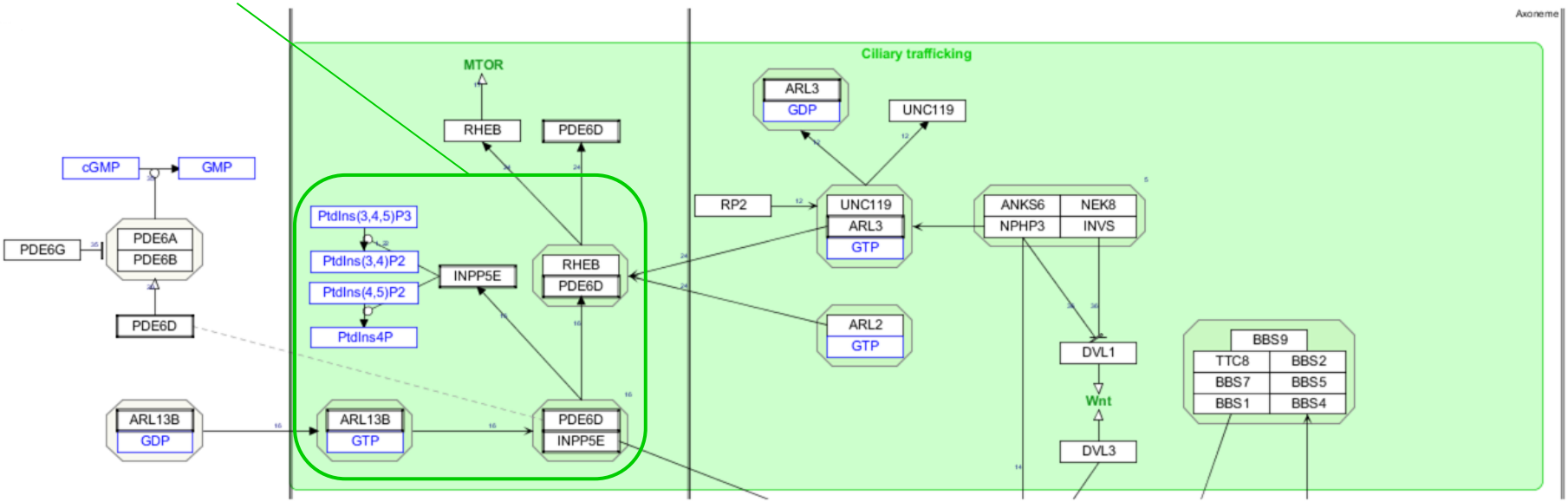
Results - Transition Zone



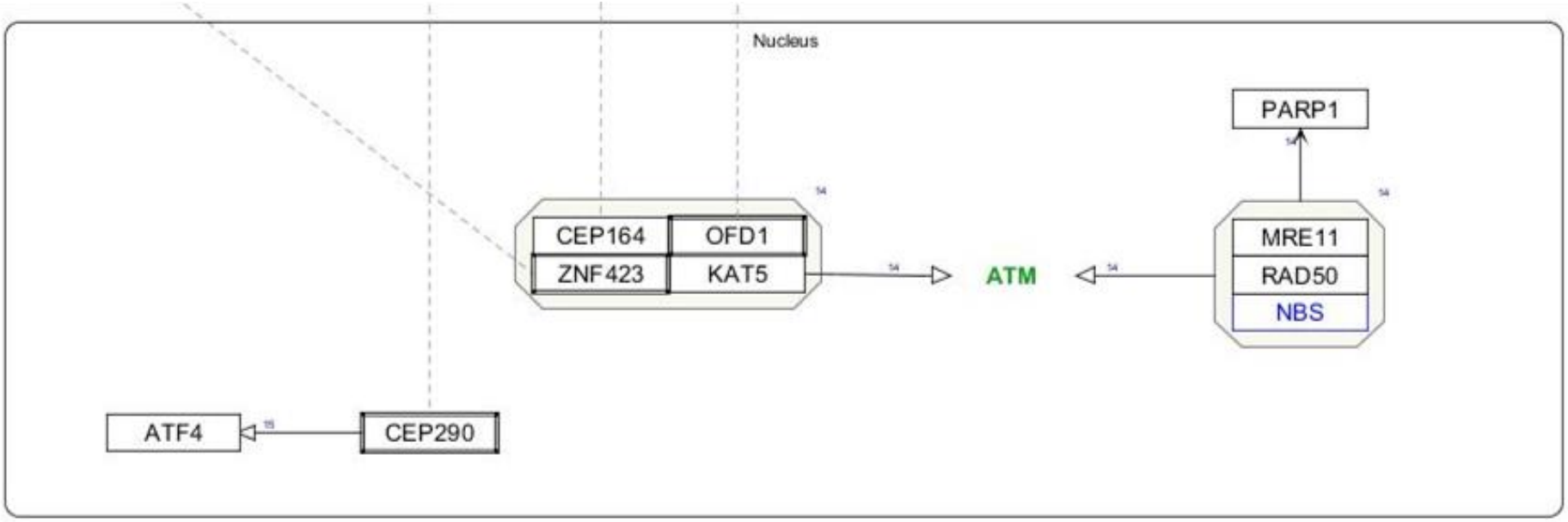
B9 ciliary complex

Results - Ciliary Trafficking

ARL13B-PDE6D-INPP5E signaling network



Results - Nucleus



Conclusion

- Three structural/functional areas
- Components of special interest
  - Centriolar satellites
  - B9 ciliary complex
  - ARL13B-PDE6D-INPP5E signaling network
- Early phases of ciliogenesis
- DNA damage response

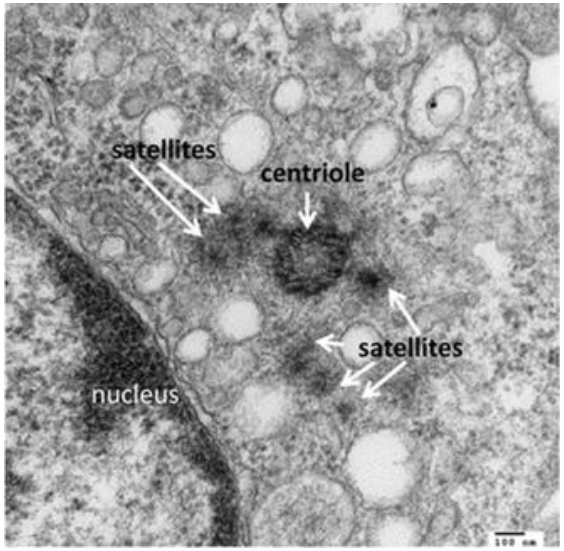


Figure 4. Microscopic image of centriolar satellites.

Figure 4. Centriolar satellites. Kloc et al., (2013). Available from https://www.researchgate.net/figure/Structure-and-molecular-composition-of-PCM-and-pericentriolar-satellites-A-An-electron_fig2_259113152.

Discussion

- Possible new insight
  - Overview involved genes
  - Many genes are functionally connected
- Exclusion certain genes
  - Lack of knowledge/relevance
- Downstream pathways
- Links to phenotype
  - Meckel Syndrome
- DNA damage response

Gene Name	***Gene Location***	***JS Type***
ARMC9	2q37.1	JBTS30
CPLANE1	5p13.2	JBTS17
CEP120	5q23.2	JBTS31
CEP41	7q32.2	JBTS15
CSPP1	8q13.1-q13.2	JBTS21
SUFU	10q24.32	JBTS32
TMEM138	11q12.2	JBTS16
PIBF1	13q21.3-q22.1	JBTS33
KIAA0586	14q23.1	JBTS23

Thank you for your attention!

Are there any questions?