New pieces of the puzzle for hereditary optic neuropathies revealed by Next Generation Sequencing

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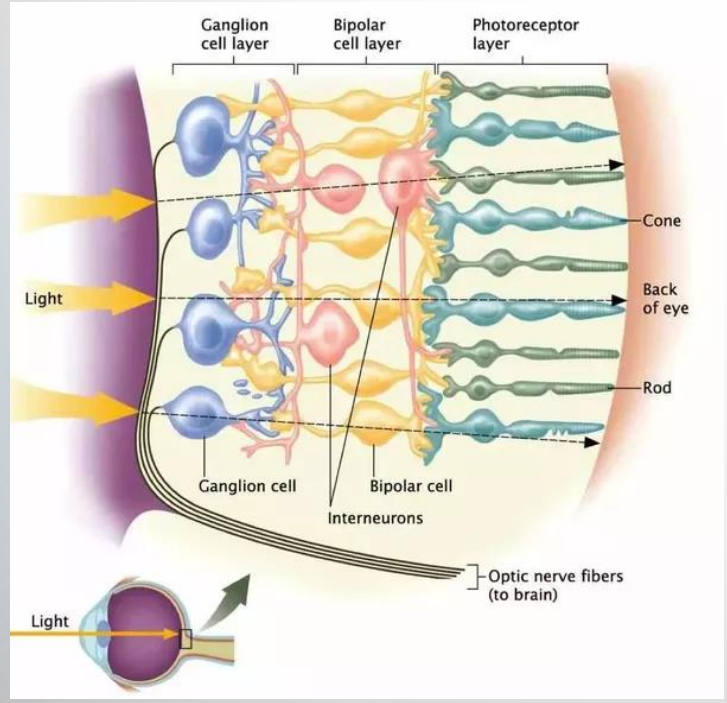
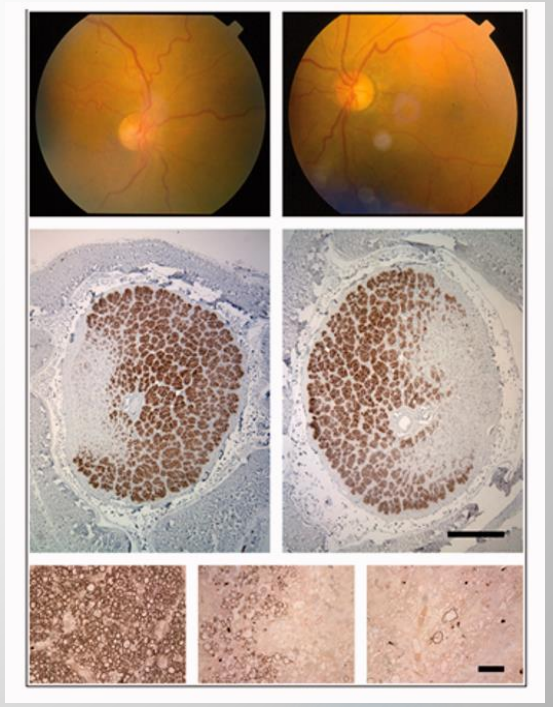
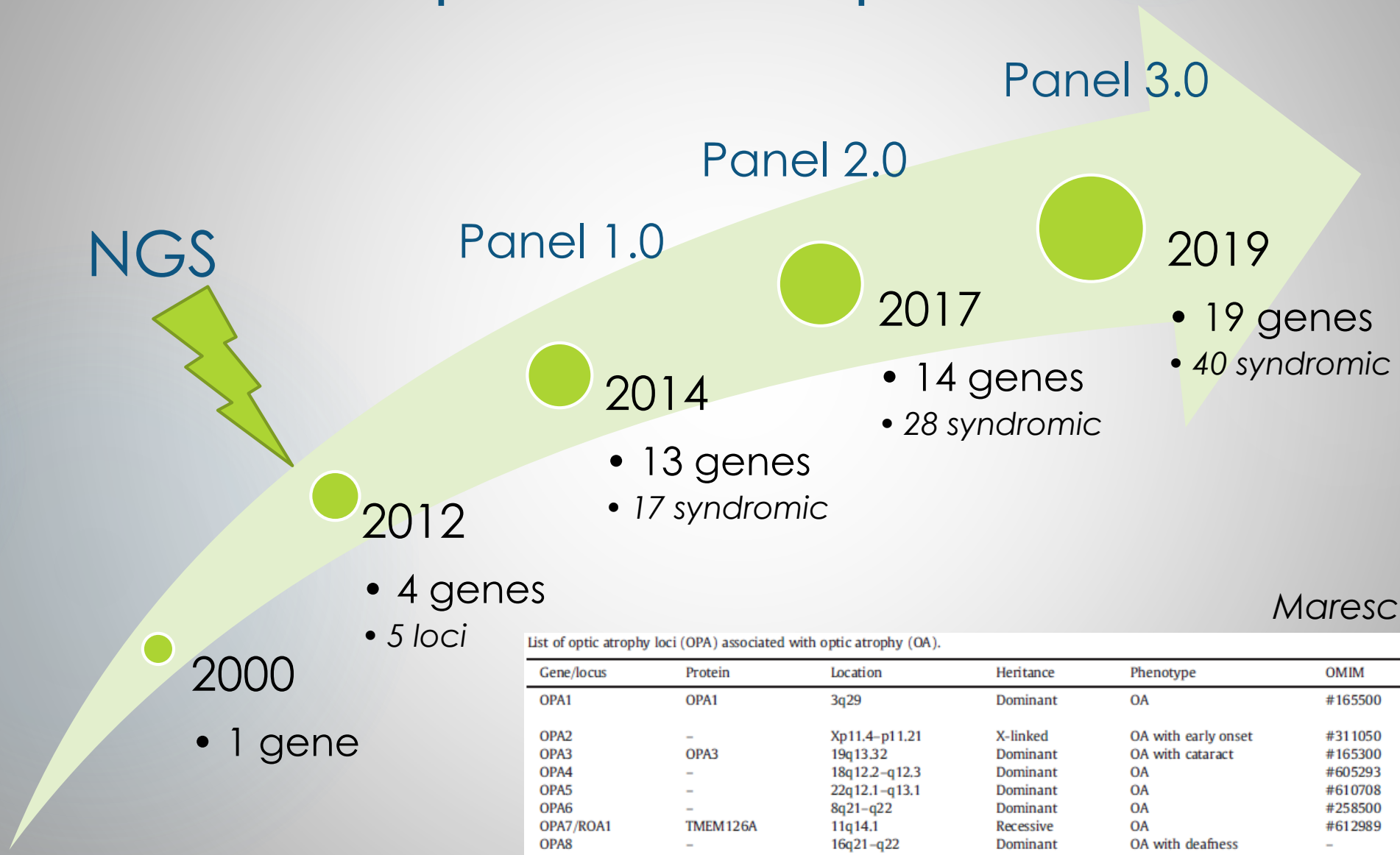
Inherited Optic Neuropathy (ION)

- Degeneration of retinal ganglion cells (RGCs)
- 50.000 people in Europe





Mendelian Optic Neuropathies



Maresca et al. 2012

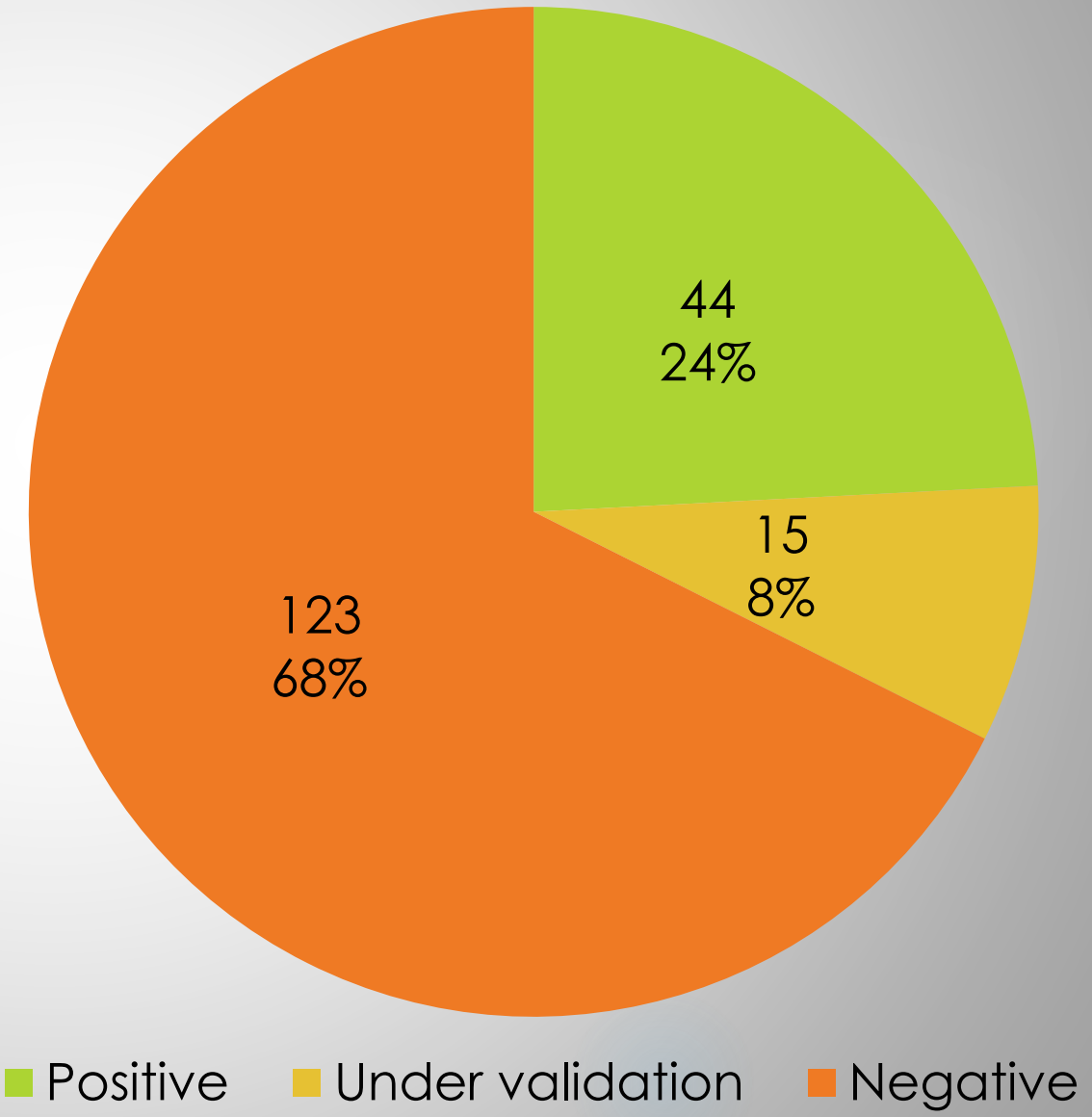
List of optic atrophy loci (OPA) associated with optic atrophy (OA).

Gene/locus	Protein	Location	Heritance	Phenotype	OMIM	Reference
OPA1	OPA1	3q29	Dominant	OA	#165500	Alexander et al. (2000); Delettre et al. (2000)
OPA2	–	Xp11.4–p11.21	X-linked	OA with early onset	#311050	Assink et al. (1997)
OPA3	OPA3	19q13.32	Dominant	OA with cataract	#165300	Reynier et al. (2004)
OPA4	–	18q12.2–q12.3	Dominant	OA	#605293	Kerrison et al. (1999)
OPA5	–	22q12.1–q13.1	Dominant	OA	#610708	Barbet et al. (2005)
OPA6	–	8q21–q22	Dominant	OA	#258500	Barbet et al. (2006)
OPA7/ROA1	TMEM126A	11q14.1	Recessive	OA	#612989	Hanein et al. (2009)
OPA8	–	16q21–q22	Dominant	OA with deafness	–	Carelli et al. (2011b)
WFS1	Wolframin	4p16.1	Dominant	OA with deafness	–	Rendtorff et al. (2011)

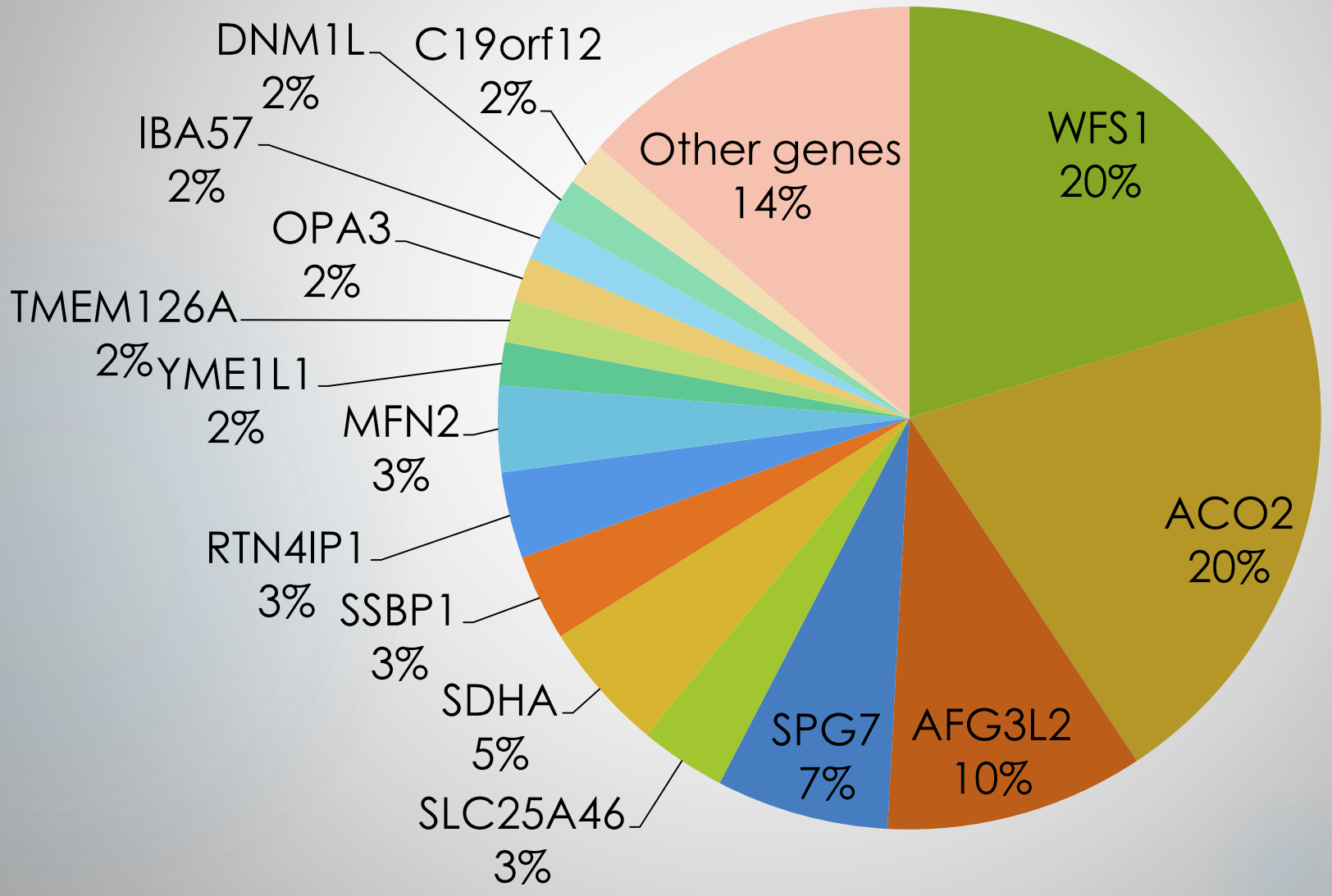
NGS panel of ION

- 185 patients with ION
- Negative for LHON and OPA1
- 2015-2019

- Amplicon based
- Enrichment based



NGS panel of ION - GENEs

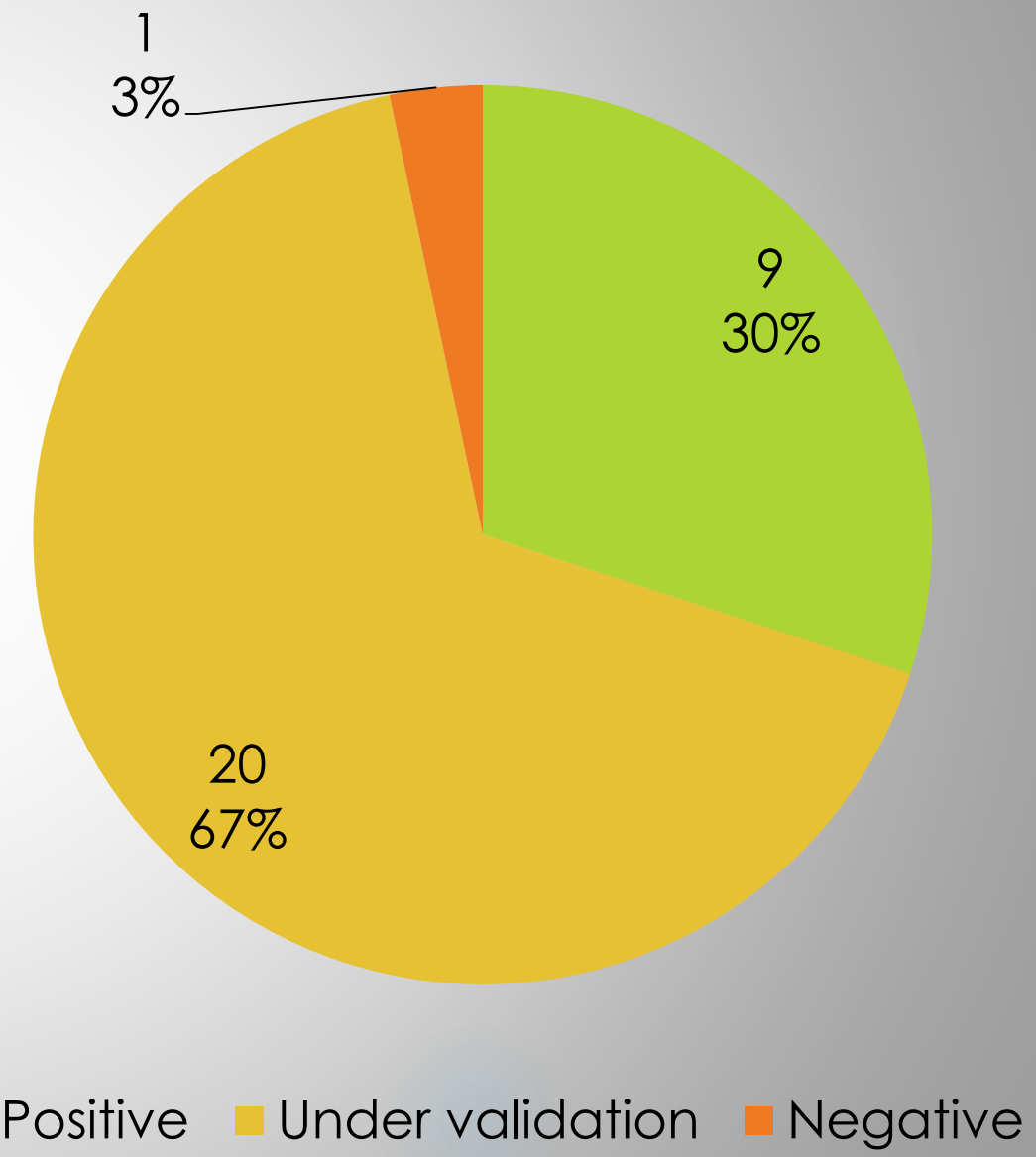


Whole Exome Sequencing of ION

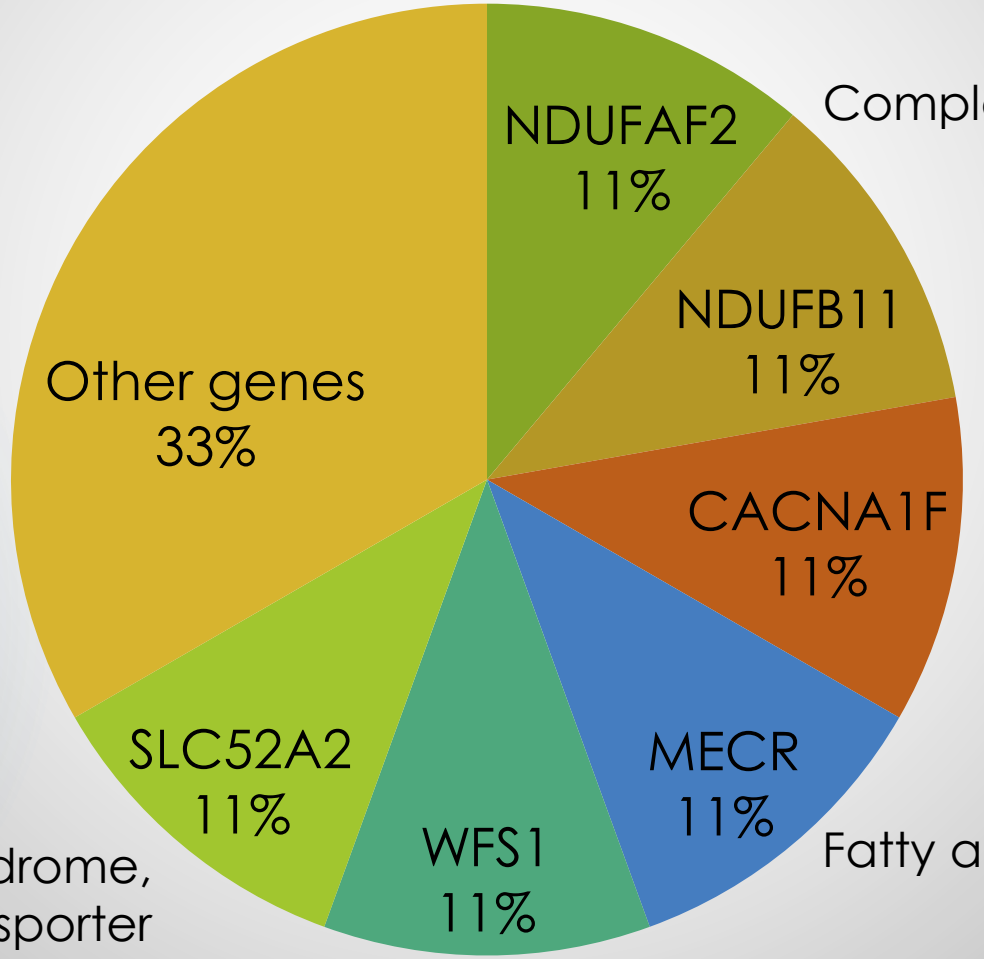
- Project of MoH GR-2016-02361449

Italian Project on Hereditary Optic Neropathies (IPHON): from genetic basis to therapy

- 30 Patients
- negative for NGS panel



exome of ION - Genes



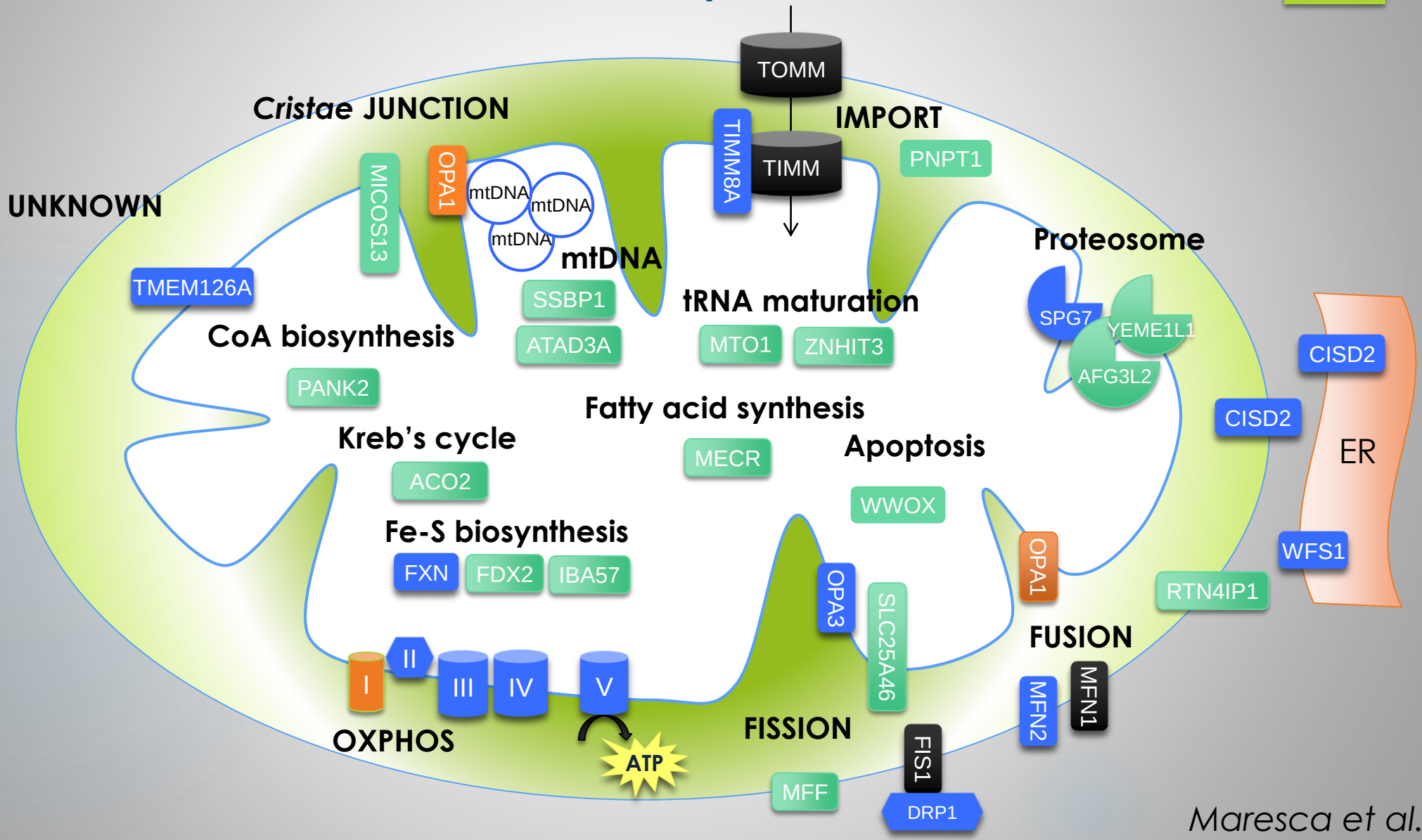
Complex I subunit

Ca^{++} channel

Fatty acid biosynthesis

Brown-Vialetto-Van Laere syndrome,
Riboflavin transporter

Mitochondrial Pathways of ION



Maresca et al. 2012

non mitochondrial Pathways of ION

- Transport
  - protein (NBAS, AP4B1, VPS53)
  - axonal (KIF1A, AP3B2)
  - riboflavin (SLC52A2)
  - Cytoskeleton (TBCD, CCDC88A)
- Cells contact (ANTXR1)
- Phospholipid translocation (ATP8A2)
- Ion Channel (CACNA1A, CACNA1F)
- Ubiquitin pathway (UCHL1)

Conclusion

- **NGS panel** are a powerful tool for diagnosis
  - 1:4 patient is genetically resolved
  - frequently updated
- **WES** are useful for new genes discovery
- new genotype/phenotype

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