Genetic background of severe/profound congenital deafness in Norway

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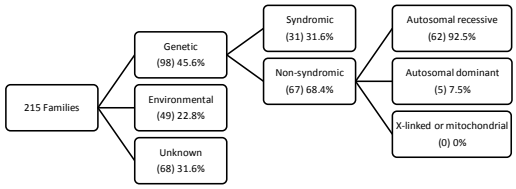
Classification of congenital hereditary hearing impairment

- According to mode of inheritance
  - Autosomal dominant
  - Autosomal recessive
  - X-linked
  - Mitochondrial
- Isolated or associated with other disorders
  - Non-syndromic
  - syndromic

Genes associated with severe/profound congenital deafness

- *GJB2* (**G**ap-**J**unction **B**eta 2) gene/Connexin26
  - digenic transmission GJB2/GJB6
- *SLC26A4* gene
  - syndromic (Pendred syndrome)
  - non-syndromic (DFNB4)
- *KCNQ1* and *KCNE1* genes
  - Jervell and Lange-Nielsen Syndrome
  - more common in Norway than elsewhere?
- The mitochondrial mutation A1555G
  - associated with antibiotic induced deafness (aminoglycosides)
- *OTOF* gene (Otoferlin)
  - associated with auditory neuropathy

Causes of congenital sensorineural deafness



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Causes of deafness

Table 1. Causes of hearing impairment

Category	Sub-category	No. of probands (%)	No. of children (%)
Hereditary non-syndromic		67 (31.2)	81 (34.8)
	Detected mutations	49	60
	GJB2 and *GJB6*	43	52
	SLC26A4	6	8
	Inner ear anomalies	10	10
	Familial hearing impairment	8	11
Syndromic		31 (14.4)	34 (14.6)
	Known	17 (54.8)	20 (58.8)
	Jervell and Lange-Nielsen	5	5
	Waardenburg	4	6
	Usher type I	2	3
	Down	2	2
	CHARGE	2	2
	Noonan	1	1
	Pendred	1	1
	Unknown	14 (45.2)	14 (41.2)
Environmental		49 (22.8)	49 (21.0)
	Prenatal or perinatal	28	28
	Meningitis	16	16
	Other infections	3	3
	Trauma	1	1
	Ototoxic	1	1
Unknown		68 (31.6)	69 (29.6)
Total		215	233

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Causes of deafness in the non-responding group

Category	*Type of syndrome*	*No. of children*
Hereditary non-syndromic		2
Syndromic	Usher type I	5[1]
	Johanson-Blizzard	1
	DiGeorge	1
	CHARGE	1
	Waardenburg	1
	Jervell and Lange Nielsen	1
	Unknown	6
Environmental	Intrauterine or perinatal etiology	6
	Meningitis	5
	Trauma	1
	Ototoxic	1
	Infectious	1
Unknown		8
Total		40

The causes of hearing loss are those compiled from patients' records
[1]Contains 2 children from the same family

Causes of deafness in all the 273 CI children

Category	Sub-category	No. of probands
Hereditary non-syndromic		69 (27%)
Syndromic		45 (18%)
	Usher type I	6
	Jervell and Lange Nielsen	6
	Waardenburg	5
	CHARGE	3
	Down (trisomy 21)	2
	Noonan	1
	Johanson-Blizzard	1
	DiGeorge	1
	Unknown	20
Environmental		63 (25%)
	Intrauterine or perinatal etiology	34
	Meningitis	21
	Trauma	2
	Ototoxic	2
	Infectious	4
Unknown		77 (30%)
Total		254

Conclusions

- Genetic causes of hearing impairment are major contributors to severe and profound deafness in Norway
- Mutations in the *GJB2* gene are commonly found in severely and profoundly deaf children in Norway
- Mutations in *SLC26A4* gene is commonly found in deaf children with inner ear malformations
- Sequencing of the *KCNQ1* gene should be considered in deaf children with suspected Jervell and Lange Nielsen syndrome.

What does the future bring?

- High throughput sequencing/Next - Generation - Sequencing
  - These techniques are already available
  - Several commercial companies offers diagnostic panels

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