Genetic Characteristics of Late-onset Pompe Disease (LOPD) in Chinese

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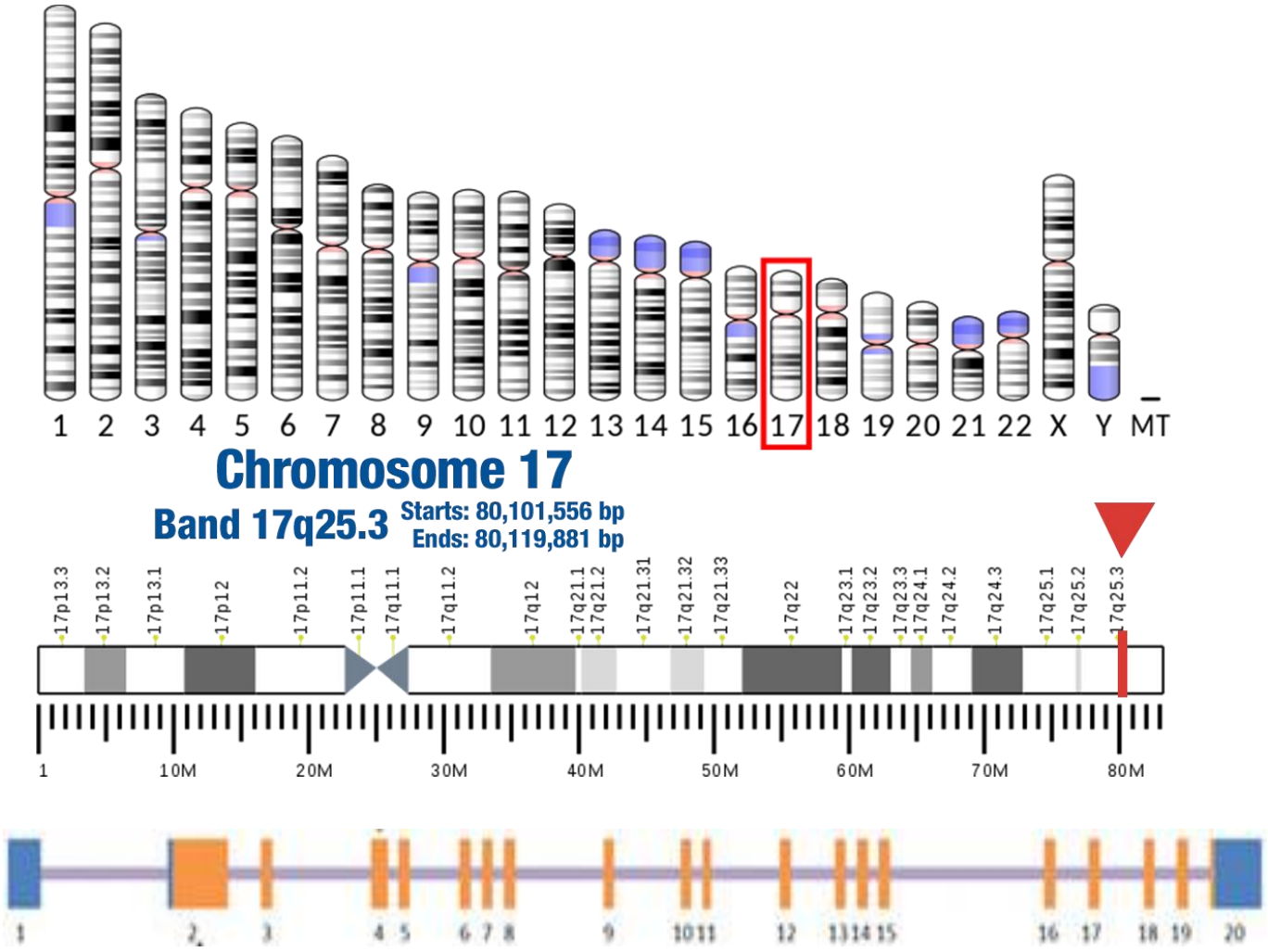
Genetics of Pompe Disease

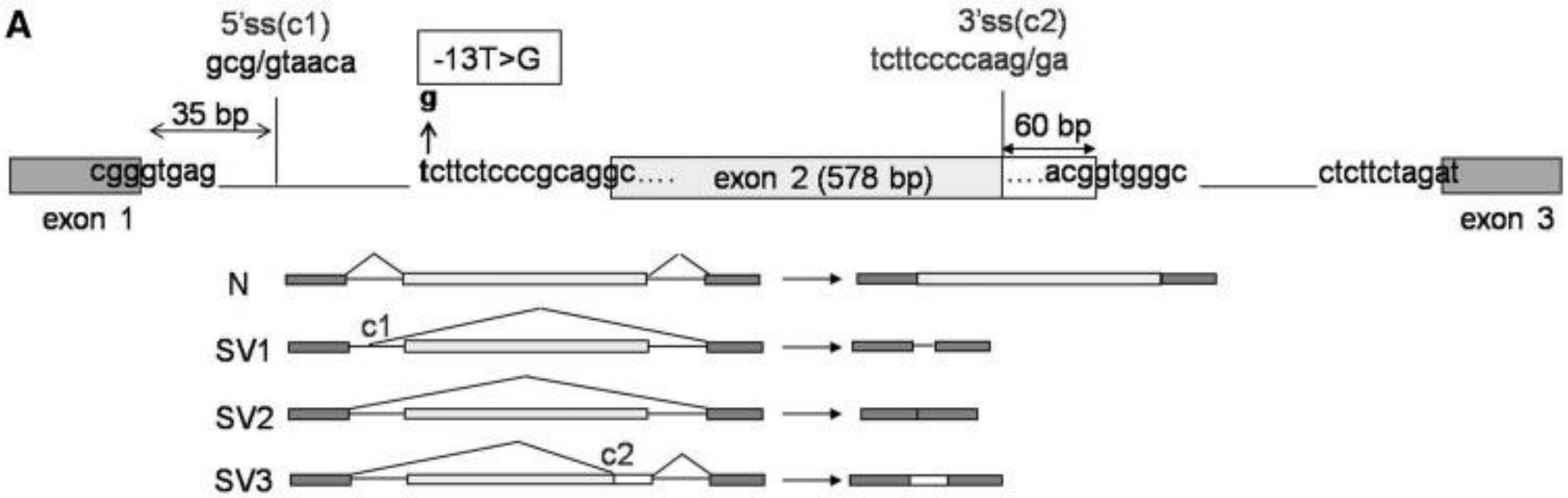
- Autosomal recessive lysosomal storage disorder due to mutations in the acid alpha-glucosidase (*GAA*) gene encoding the lysosomal alpha-glucosidase. This genetic defect leads to the deficient activity of lysosomal alpha-glucosidase resulting in impaired glycogen degradation and accumulation within the lysosomes.
- The *GAA* gene is localized to chromosome 17q25.2-q25.3 and it was cloned and sequenced in 1991. The *GAA* gene is approximately 28 kb and encompasses 20 exons. The first amino acid is encoded by the exon2.
- As of 14 Oct 2023, 911 *GAA* variants have been listed in the Pompe disease database (www.pompevariantdatabase.nl)



Prevalent *GAA* pathogenic variants world-wide

Ethnicities	*GAA* variant 1	*GAA* variant 2	Reference
Caucasians	c.-32-13T>G (p.?)		Huie, M L et al. *Human molecular genetics* vol. 3,12 (1994): 2231-6.
Korean (18 pts)	c.1316T>A (p. Met439Lys)	c.1857C>G (p.Ser619Arg)	Park, Hyung-Doo et al. *Annals of clinical and laboratory science* vol. 43,3 (2013): 311-6.
Japanese (38 pts)	c.546G >T (p.Thr182=)	c.1857C>G (p.Ser619Arg)	Fukuhara, Yasuyuki et al. *Molecular genetics and metabolism reports* vol. 14 3-9. 31 Oct. 2017.
Indian (64 pts)	c.1933G>A (p.Asp645Asn)	c.1A>G (p.Met1Leu)	Thomas DC et al. Novel and frequent pathogenic variants in a large cohort of Indian patients of Pompe, Fabry, Gaucher and Hurler disease. *Clin Biochem*. 2021;89:14-37.
Iranian (14 pts)	c.-32-13T>G (p.?)		Nazari F, Sinaei F, Nilipour Y, et al. Late-onset pompe disease in Iran: A clinical and genetic report. *Muscle Nerve*. 2017;55(6):835-840.

GAA c.-32-13T > G is the most common mutation in Caucasian individuals



Genetic Characteristics of Late-onset Pompe Disease in Taiwan Chinese

- **Patients:** 15 LOPD patients (1993-2009, Taipei).
- **Results:**

-median age of onset was 15 (12-35) years, median age at diagnosis was 21 (10-38) years, 8 patients (53%) required mechanical ventilation.

-manifestations: proximal muscle weakness, respiratory insufficiency, hyperCKemia

-Mutation analysis revealed that the two dual mutations in the *GAA* c.[1935C>A; 1726G>A] (p.[D645E; G576S]) and c.[2238G>C; 1726G>A] (p.[W746C; G576S]). represented 66.5% of the mutated chromosomes.

-*GAA* c.1726G>A pseudodeficiency mutation significantly decreased the residual enzyme activity of c.2238G>C. Most patients responded poorly to recombinant human GAA.

- **Conclusions:** Taiwan Chinese patients with late-onset Pompe disease often showed onset of symptoms in their second decade of life with rapid disease progression, which is probably due to a specific pattern of *GAA* mutation. Therefore, early diagnosis and early treatment would be necessary to improve the prognosis of these patients.

Yang, Chih-Chao et al. “Rapid progressive course of later-onset Pompe disease in Chinese patients.” *Molecular genetics and metabolism* vol. 104,3 (2011): 284-8.

Genetic Characteristics of Late-onset Pompe Disease in Northern Mainland Chinese

- **Patients:** 27 (9 male+18 female) LOPD patients from 24 families (2003-2013, Beijing).
- **Results:**

-median age of onset: 21 (1.2-32) years, median age at diagnosis: 22 (3-35) years.

-manifestations: proximal muscle weakness, respiratory insufficiency, hyperCKemia

-15/27 (55.5%) patients have respiratory dysfunction, 11/15 (73.3%) patients require nocturnal ventilation support.

-*GAA* mutation analysis revealed 26 different mutations, including 10 that were novel. The allelic frequency of c.2238G>C (p.W746C) was found to be 27.08% in this patient group.

- **Conclusions:** Our findings indicate that c.2238G > C (p.W746C) is the most common mutation in mainland Chinese late-onset Pompe patients, as observed in Taiwanese patients. The novel mutations identified in this study expand the genetic spectrum of late-onset Pompe disease, and the prevalence of respiratory dysfunction highlights the importance of monitoring pulmonary function in late-onset Pompe patients.

Liu X, Wang Z, Jin W, et al. Clinical and GAA gene mutation analysis in mainland Chinese patients with late-onset Pompe disease: identifying c.2238G > C as the most common mutation. *BMC Med Genet*. 2014;15:141.

Genetic Characteristics of Late-onset Pompe Disease in Mainland China from Pompe Registry

- **Patients:** 59 (30 male+29 female) LOPD (2013-2016, Beijing, Shanghai, Guangzhou and Jinan)
- **Results:**

- age of onset: 14.9 years, median age at diagnosis: 22.1 years.

-manifestations: respiratory and musculoskeletal: shortness of breath after exercise (82%), receipt of respiratory support (52%), proximal muscle weakness in lower extremities (87%), ambulatory difficulty (69%), muscle weakness in trunk (67%), and proximal muscle weakness in upper extremities (57%).

-*GAA* mutation analysis revealed *GAA* c.2238G>C (n = 18, 58.1%) and c.2662G>T (n = 5, 16.1%)

- **Conclusions:** The most common mutations were *GAA* c.2238G>C and c.2662G>T.

Zhao Y, Wang Z, Lu J, et al. Characteristics of Pompe disease in China: a report from the Pompe registry. *Orphanet J Rare Dis*. 2019;14(1):78.

Genetic Characteristics of Late-onset Pompe Disease in Eastern Mainland Chinese

- **Patients:** 14 (7 male+7 female) LOPD patients from 24 families (2017-2021, Nanjing).
- **Results:**

-mean age of onset: 15 (7-36) years, mean age at diagnosis: 22 (8-47) years.

-manifestations: proximal muscle weakness, respiratory insufficiency, GI dysfunction such as intermittent diarrhoea

-*GAA* mutation analysis revealed 17 different mutations, including 4 that were novel. The allelic frequency of c.2238G>C (p.W746C) was found to be 14.3% in this patient group.

- **Conclusions:** *GAA* c.2238G > C (p.W746C) is the most common mutation in eastern mainland Chinese late-onset Pompe patients.

Zhao HH, Ma Z, Ying ZX, et al. Clinical manifestations and acid alpha-glucosidase mutation characterisation of a cohort of patients with late-onset Pompe disease in eastern China. *Ann Transl Med*. 2021;9(24):1803.

Genetic Characteristics of Late-onset Pompe Disease in Hong Kong Chinese

- **Patients:** 11 (6 male+5 female) LOPD patients from 6 families (2000-2013, Hong Kong).
- **Results:**

-mean age of onset: 20.5 (6-44) years, mean age of diagnosis 27.5 (9-44) years

-manifestations: reduced ET and SOB at night, weakness, fatigue, etc

-*GAA* mutation analysis revealed 7 different mutations: c.1082C>T, c.1309C>T, c.1634C>T, c.1935C>T, c.2014C>T, c.2238G>C and c.1411_1414del

- **Conclusions:** *GAA* c.1309C>T, c.1935C>A and 2238G > C are the most common mutations in Hong Kong Chinese late-onset Pompe patients.

GAA c.2238G>C (p.Try746Cys) is the most common mutation in Chinese LOPD patients

Region	Patient Number	Most common *GAA* mutation(s)	Reference
Taiwan (Taipei)	15	c.1935G>A c.2238G>C	Yang CC, et al. *Molecular genetics and metabolism* vol. 104,3 (2011): 284-8.
Northern China (Beijing)	29	c.2238G>C	Liu X, et al. *BMC Med Genet*. 2014;15:141
Eastern China (Nanjing)	14	c.2238G>C	Zhao HH, et al. *Ann Transl Med*. 2021;9(24):1803
Mixed China (Beijing, Shanghai, Guangzhou and Jinan)	59	c.2238G>C c.2662G>T	Zhao Y, et al. *Orphanet J Rare Dis*. 2019;14(1):78.
Hong Kong	10	c.1309C>T c.1935C>A c.2238G >C	Chu YP, et al. *Neuromuscul Disord*. 2016;26(12):873-879.

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