Recurrent Pathogenic *LMNA* Gene Variant Causes Mandibuloacral Dysplasia in a Ghanaian Multiplex Family

Daniel Amewoalor[1], Victoria Damoah Baffoe[2], Gideon Okyere Mensah[1], Charles Martyn-Dickens[2], Bruce Tsri[1], Josephine Oduro Tweneboah[2], Christian Opoku Asamoah[1], Daniel Kwesi Sabbah[3], Esther Annette Tawiah[2], Gyikua Plange-Rhule[2,4], Tamara Busch[5], Solomon Obiri-Yeboah[3], Azeez Butali[5], Anne Hing[6], Peter Donkor[7], Lord Jephthah Joojo Gowans[1,3]

[1]Department of Biochemistry and Biotechnology, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana,[2]Directorate of Child Health, Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana, [3]School of Dentistry, KNUST, Kumasi, Ghana,[4]Department of Child Health, School of Medical Sciences, KNUST, Kumasi, Ghana,[5]Department of Oral Pathology, Radiology and Medicine, College of Dentistry, University of Iowa, Iowa City, USA.,[6]Department of Pediatrics, Division of Craniofacial Medicine, University of Washington, Seattle, WA, USA.,[7]Department of Surgery, School of Medical Sciences, KNUST, Kumasi, Ghana.

Correspondence: Ljj.gowans@gmail.com

Introduction

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive, progeroid laminopathy with a postnatal age of manifestation typically occurring between 2 and 3 years[1].

MAD is characterised clinically by accelerated ageing phenotypes, skeletal abnormalities and lipodystrophy[1,2].

MAD type A (MADA) and MAD type B (MADB) result from homozygous or compound heterozygous mutations in the *LMNA* and *ZMPSTE24* genes, respectively[1,2].

The clinical phenotypes of laminopathies are heterogeneous and overlap

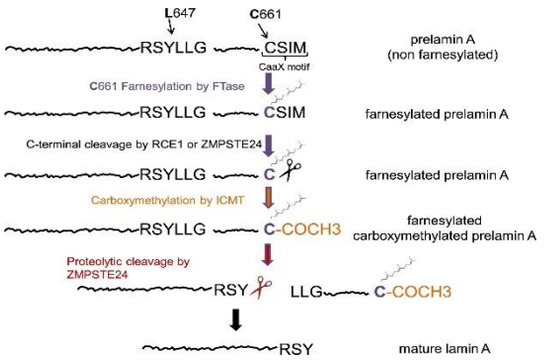

Fig.1 Post-translational modification of prelamin A into mature lamin A under nonpathological conditions[2].

Aims of Study

- Decipher the genetic aetiology of progeria in a Ghanaian multiplex family
- Ascertain the phenotypic presentation of MADA in the multiplex family

Subjects and Methods

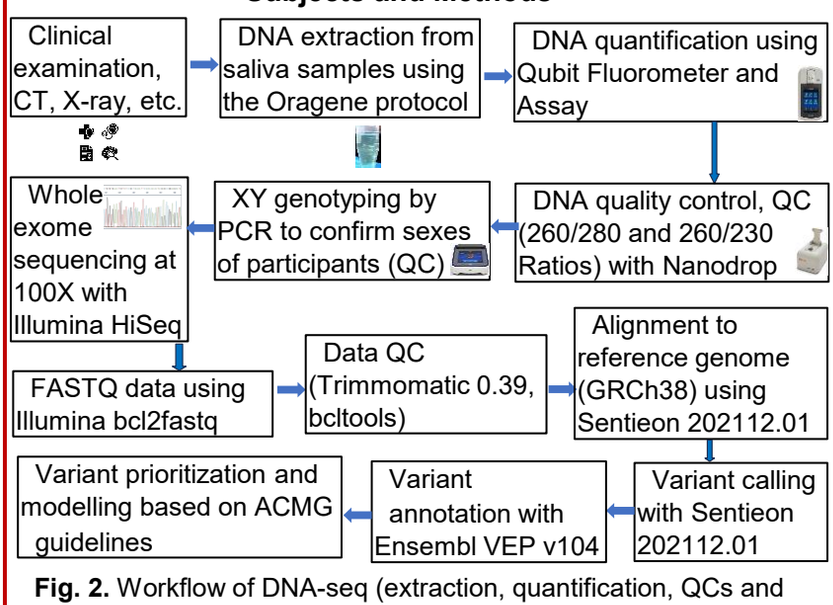

Fig. 2. Workflow of DNA-seq (extraction, quantification, QCs and whole exome sequencing and bioinformatics analysis)

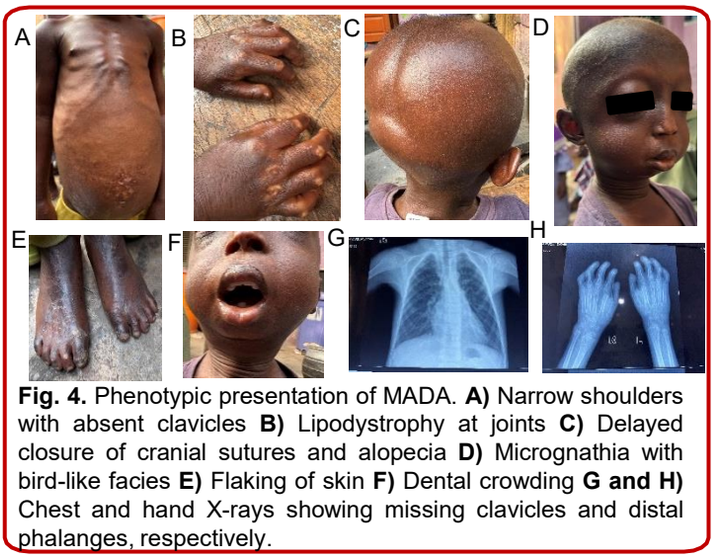

Fig. 4. Phenotypic presentation of MADA. **A)** Narrow shoulders with absent clavicles **B)** Lipodystrophy at joints **C)** Delayed closure of cranial sutures and alopecia **D)** Micrognathia with bird-like facies **E)** Flaking of skin **F)** Dental crowding **G and H)** Chest and hand X-rays showing missing clavicles and distal phalanges, respectively.

Fig. 5. Multiple sequence alignment of Prelamin A with Clustal Omega shows the evolutionary conservation of the lamin tail domain amongst different organisms. The amino acid change (p.R527C) is highlighted.

Results and Discussions

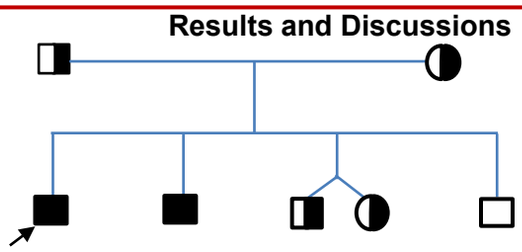

Fig. 3. The pedigree of the family. This pedigree illustrates inheritance of the variant (ENST00000368300.9:c.1579C>T, p.Arg527Cys) in the *LMNA* gene. The proband is homozygous for the variant, while both parents are carriers. Among the siblings, two are heterozygous, one is homozygous for the variant, and one has the wild-type gene.

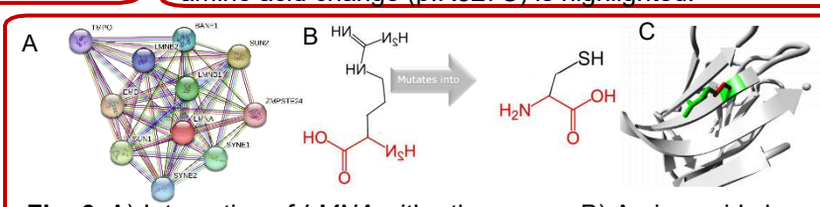

Fig. 6. A) Interaction of *LMNA* with other genes B) Amino acid change and conformational analysis using HOPE webserver C) Schematic showing the wildtype (green) and mutant (red) residues

Conclusion and Recommendations

- The WES identified a recurrent missense variant that causes MADA
- The study highlights the first documented genetic evidence of MADA in a Ghanaian family
- Genetic testing and counselling is highly recommended in Ghana

References

1. Schnabel, F., Kornak, U. & Wollnik, B. Premature aging disorders: A clinical and genetic compendium. *Clin. Genet.* **99**, 3–28 (2021).
2.Cenni, V. *et al.* Mandibuloacral dysplasia: A premature ageing disease with aspects of physiological ageing. *Ageing Res. Rev.* **42**, 1–13 (2018).