NPR2 gene mutations associated with acromesomelic dysplasia Maroteaux type are mostly unique to families

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Acromesomelic dysplasia Maroteaux type (AMDM) (OMIM 602875) is a rare autosomal recessive skeletal dysplasia with an estimated prevalence of 1/1,000, 000. It is characterised by severe dwarfism with shortening of the middle and distal segments of the limbs. Although the patients have normal length and weight at birth, a skeletal disorder can be suspected by one year of age. Mutations in the *NPR2* gene which encodes for the natriuretic peptide receptor B (NPR-B) is the underlying genetic cause of this disorder.

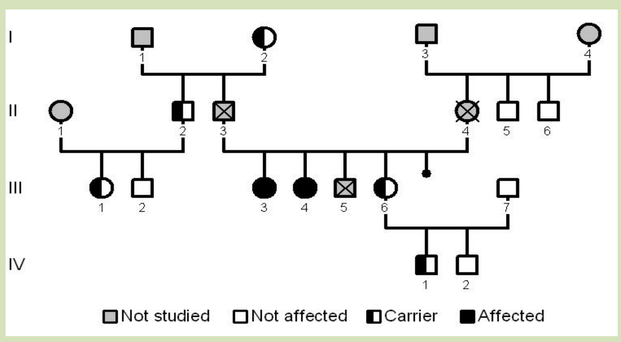
Objective: Genetic confirmation of AMDM and the identification of the causal mutations in *NPR2* gene

Methods: A total of 8 Individuals, belonging to 7 families, diagnosed of AMDM plus relatives were referred from UK, France, India and Spain for genetic analysis. The patients fulfilled clinical and radiological criteria of AMDM and the informed consent was obtained. Molecular genetic study: DNA was extracted from peripheral blood leukocytes by standard techniques. All the coding exons as well as intro-exon boundaries of *NPR2* gene were amplified and directly sequenced by Sanger method.

Results: The clinical diagnosis was genetically confirmed in all the patients. Ten novel mutations were identified and each mutation was unique for each patient (P) or family (F). For the description of the genotypes of the patients see the table 1. Electropherograms of mutations from families 1, 2, 3 & 4; see figures 1,2,3,4.

FAMILY 1

Two affected siblings: III.3 and III.4 of 35 and 34 years of age respectively. They came from Northwest of Spain .The patients suspected consanguinity in the family few generations ago but it could not be proven.
III.3: Normal weight and length at birth. The affected phenotype was detected by one year of age. Final height: 120 cm. III.4: Normal weight and length at birth. The affected phenotype was detected before one year. Final height: 107.4 cm.



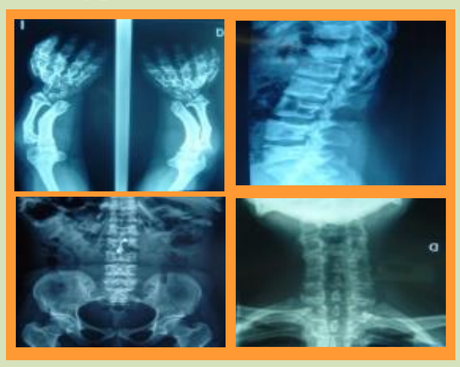
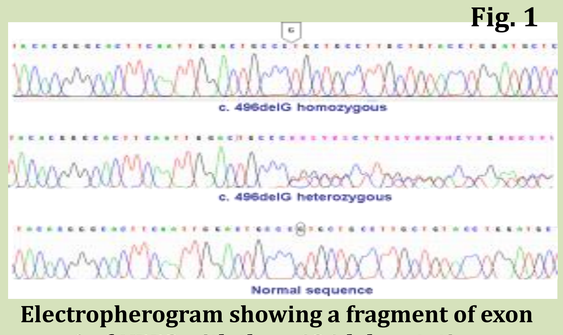


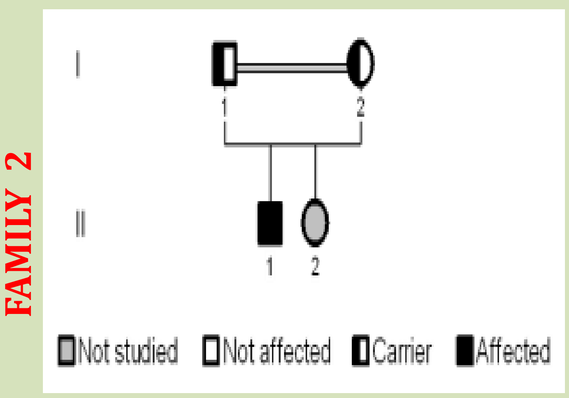
Fig. 1

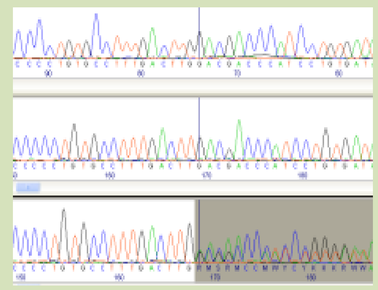


Electropherogram showing a fragment of exon 1 of *NPR2* with the c.494del mutation

FAMILY 2

II.1 AMDM affected boy of 6 years 3 months of age. II.2 girl with similar phenotype who was not genetically studied. Parents were consanguineous .They came from the UK.





c.1330del homozyhous and heterozygous mutation in exon 6 (midle and lower respectively)

Fig. 2

FAMILY 3

One year 3 months old girl with clinical suspition of AMDM. Parents were not consanguineous. They came from France.

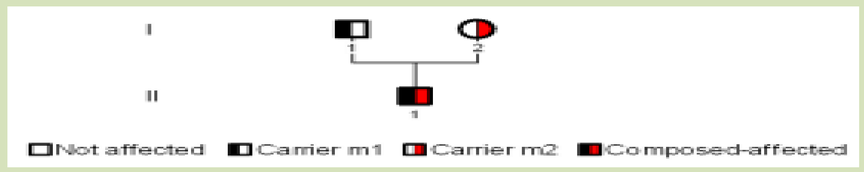
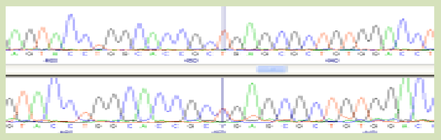
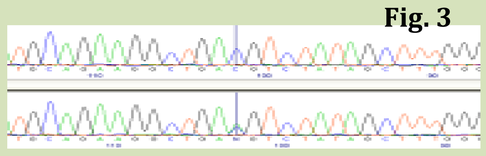


Fig. 3



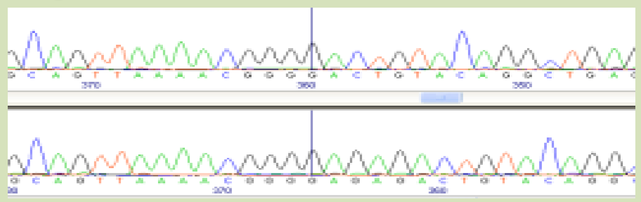
c.245T>C heterozygous mutation in exon 1 (lower)



c.2118C>A heterozygous mutation in exon 14 (lower)

FAMILY 4

18 years old AMDM affected men. Hight 116 cm. No data about his family. He came from the Maghreb.



c.2548-2551del homozygous mutation in exon 17 (lower)

Fig. 4

P	F	Mutation at cDNA level (Ref Sec NM_003995.3)	Mutation at protein level
1	1	c.[494del];[494del]	p.[Arg165Leu*fs**80]; [Arg165Leu*fs**80];
2	1	c.[494del];[494del]	p.[Arg165Leu*fs**80]; [Arg165Leu*fs**80];
3	2	c.[1330del];[1330del]	p.[Asp444Thr*fs**33];[Asp444Thr*fs**33]
4	3	c.[245T>C];[2118C>A]	p.[Leu82Pro];[Asp706Glu]
5	4	c.[2548_2551del];[.2548_2551del]	p.[Glu850Leu*fs**32];[Glu850Leu*fs**32]
6	5	c.[1124G>A];[1124G>A]	p.[Gly375Asp];.[Gly375Asp]
7	6	c.[1084_1089del];[2137A>T]	p.[Leu362_Arg363del];[Ile713Phe]
8	7	c.[1351+7G>A];[2107C>T]	p.[?];[Gln703*]

P:patient/ F:family

Table 1

Conclusions:

- 1)We have identified ten novel mutations in *NPR2* as the cause of AMDM, which broadens the spectrum of inactivating mutations in this gene.
- 2) These *NPR2* mutations are “private”: unique to individuals and/or families.
- 3)The identification of the causal mutation in AMDM is important not only to confirm the clinical and radiological diagnosis but to enable a proper genetic counseling and an eventual prenatal diagnosis.

* The authors declare that there are no conflicts of interest

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