Familial Neurohypophyseal Diabetes Insipidus in 13 kindreds and 2 Novel Mutations in the Vasopressin Gene

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BACKGROUND and AIM

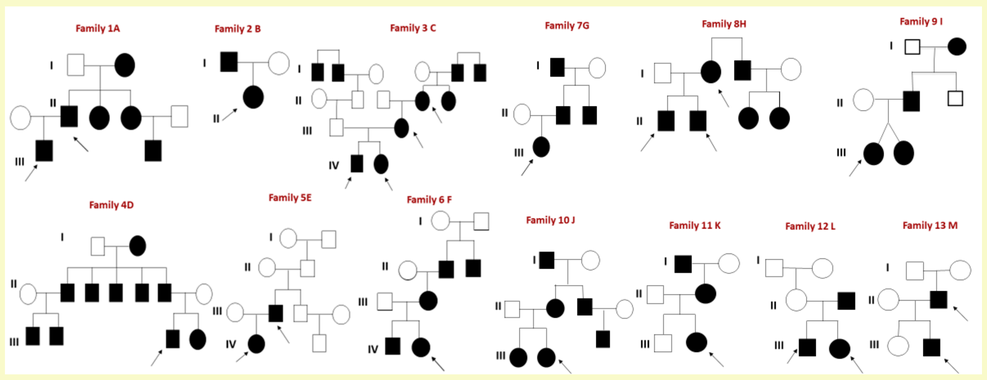
Autosomal dominant neurohypophyseal diabetes insipidus (adNDI) is caused by arginine vasopressin (AVP) deficiency resulting from mutations in the AVP-NPII gene encoding the AVP preprohormone.

Aim: To describe the clinical and molecular features of Italian unrelated families with central Diabetes Insipidus (CDI).

SUBJECTS and METHODS

We analyzed AVP-NPII gene in 13 families in whom CDI appeared to be segregating **(Figure 1)**.

Figure 1. Pedigrees of the 13 families (A-M).



Patients with genetic diagnosis are indicated by the arrows

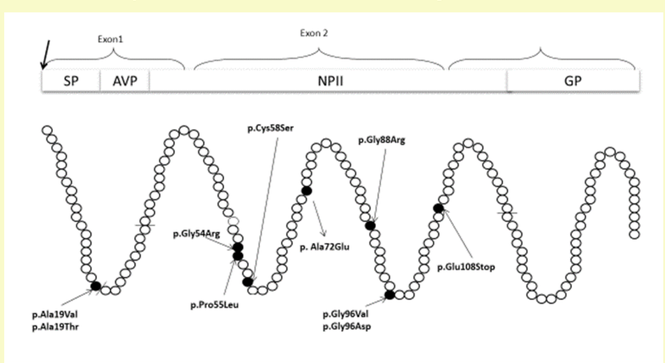
RESULTS

- n=22 patients were found to carry a pathogenic AVP-NPII gene mutation **(Table 1);**
- n=2 novel c.173 G>C (p.Cys58Ser), c.215 C>A (p.Ala72Glu) missense mutations and additional n=8 different mutations previously described were identified; n=9 were missense and n=1 non sense mutation;
- median age at CDI onset was 32.5 months with a variability within the same mutation (3 to 360 months).

Table 1. Available Age of onset in index-cases and family members of our families and AVP mutations detected in 22 subjects

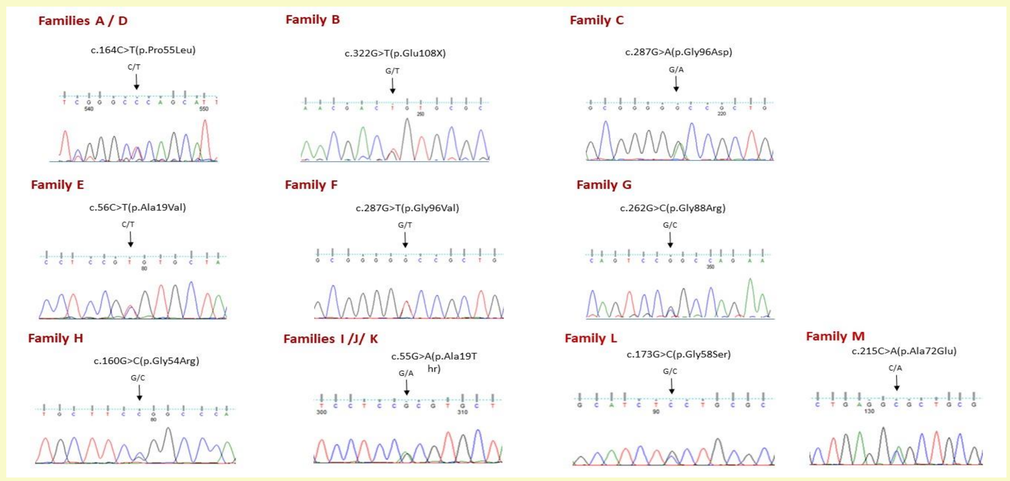
Families	Age of onset (months)	Mutation/Exon
Family A: index-case Family A: father	32 nd	c.164C>T – (p.Pro55Leu) c.164C>T – (p.Pro55Leu) **Exon II**
Family B: index-case Family B : father	30 72	c.322G>T – (p.Glu108X) **ExonII**
Family C: index-case Family C: index-case Family C: mother Family C: grandmother	16 12 24 360	c.287 G>A – (p.Gly96Asp) c.287 G>A – (p.Gly96Asp) c.287 G>A – (p.Gly96Asp) c.287 G>A – (p.Gly96Asp) **ExonII**
Family D: index-case Family D: sister	33 22	c.164C>T – (p.Pro55Leu) **ExonII**
Family E: index-case Family E: father	24 18	c.56C>T (p.Ala19Val) c.56C>T (p.Ala19Val) **Exon I**
Family F: index-case Family F: brother Family F: mother	36 36 72	c.287G>T – (p.Gly96Val) **ExonII**
Family G; index-case	NA (first years of life)	c.262G>C – (p.Gly88Arg) **ExonII**
Family H: index-case Family H: index-case Family H : mother	17 19 NA (childhood)	c.160G>C – (p.Gly54Arg) c.160G>C – (p.Gly54Arg) c.160G>C – (p.Gly54Arg) **ExonII**
Family I -index-case Family I- index-case	120 120	c.55G>A – (p.Ala19Thr) **Exon I**
Family J- index-case	120	c.55G>A – (p.Ala19Thr) **Exon I**
Family K- index-case	132	c.55G>A – (p.Ala19Thr) **Exon I**
Family L- index-case Family L- brother	132 120	c.173 G>C – (p.Cys58Ser) c.173 G>C – (p.Cys58Ser) **ExonII**
Family M- index-case Family M-father	3 6	c.215 C>A – (p. Ala72Glu) c.215 C>A – (p. Ala72Glu) **Exon II**

Figure 2. Schematic diagram of the coding regions of the AVP-NPII gene
The location and type of mutations associated with familial central diabetes insipidus identified in our cohort are represented and indicated by the arrows.



- No clear genotype-phenotype correlation has been observed, except for the c.55 G>A (p.Ala19Thr) mutation, which led to a later onset of disease (median age 120 months).

Figure 3. Sequencing chromatograms obtained by automated dye-terminator sequencing of the AVP-NPII gene in the affected subjects

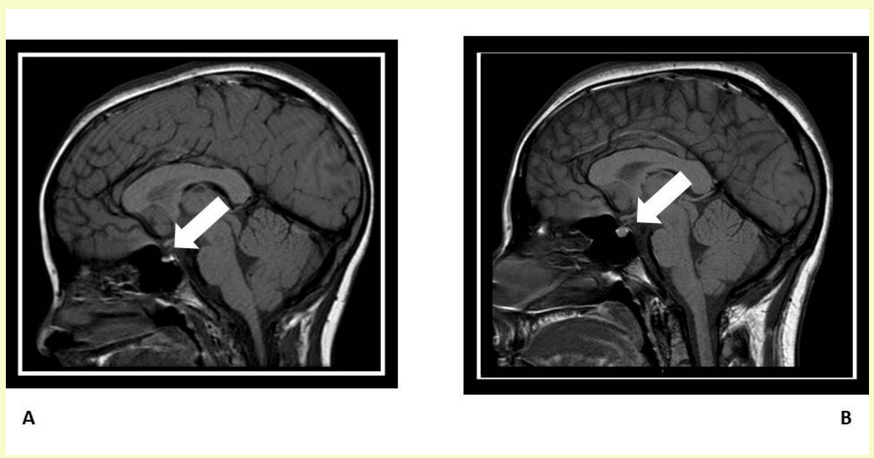


- Brain magnetic resonance imaging (MRI) revealed absence of posterior pituitary hyperintensity in 8 out of 15 subjects, hypointense signal in 4 and normal signal in 2 **(Table 2).**
- Follow-up MRI showed the disappearance of the posterior pituitary hyperintensity after 6 years in one case **(Fig.4).**

Table 2. MRI findings in the subjects with AVP-NPII gene mutations

Families	Members	Anterior Pituitary	Pituitary Stalk	Posterior Pituitary Signal
1A	Index-case III1	Normal	Normal	Undetectable
2B	Index-case II1	Normal	Normal	Undetectable
3C	Index-case IV1 Mother- III2	Hypoplasia Normal	Normal Normal	Undetectable Undetectable
4D	Index-case III3 Sister III4	Normal Normal	Normal Normal	Normal Hypointense
5E	Index-case IV1 Index-case MRI follow-up	Hypoplasia Hypoplasia	Normal Normal	Normal Undetectable
6F	Index-case IV2 Brother IV1 Mother III2	Normal Normal Empty sella	Normal Normal Normal	Hypointense Undetectable Hypointense
7G	Index-case	Normal	Normal	Hypointense
8H	Index-case II1	Normal	Normal	Undetectable
11K	Index-case	Normal	Normal	Not available
12 L	Index-case	Normal	Normal	Hypointense
13M	Index-case	Normal	Normal	Undetectable

Figure 4. Sagittal T1-weighted MRI in patient E.
A. Normal anterior pituitary and pituitary stalk size, and normal posterior pituitary hyperintensity (PPI) (white arrow) at the time of first MRI.
B. Pubertal pituitary hypertrophy, normal pituitary stalk size and decreased signal intensity of the PPI at the age of 13 years (6 years after the first MRI).



CONCLUSIONS

adNDI is a progressive disease with a variable age of onset. Molecular analysis of AVP-NPII gene and counseling should be provided in selected cases to avoid unnecessary investigations and to ensure an early and adequate treatment.

References

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58ESPE P1-097
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