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Is Whole Exome Sequencing (WES) Sufficient to Elucidate the Genetic Aetiology of Primary Enuresis Nocturna: The First Molecular-Based Large Family Study and a Brief Literature Review

Tüm Ekzom Dizileme (WES), Primer Enürezis Nokturna'nın Genetik Etiyolojisini Aydınlatmak İçin Yeterli Midir: İlk Moleküler Temelli Geniş Aile Çalışması ve Kısa Bir Literatür Derlemesi

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ABSTRACT

Objectives: Enuresis nocturna is a condition that negatively affects quality of life in childhood and adulthood. Primary enuresis nocturna (PEN) is a condition in which bedwetting continues after the age of five without a dry period. PEN is called non-monosymptomatic (PNMEN) when lower urinary tract findings are present and monosymptomatic (PMEN) when they are absent. Studies on the etiology of PEN, the 4p, 8q, 12q, 13q, 22q chromosomal regions, *GNAZ, DRD5, D1B, NOS1, DRD4, PRDM13, SIM1, EDNRB, AQP2* genes, rs9376454, rs60721117 variants have been proposed as genetic responsible. Here, it is aimed to clarify the genetics of enuresis by analysing the sociodemographic and genetic findings of a large family with PEN.

Materials and Methods: Detailed anamnesis of the family was taken, physical examinations, ultrasonography, voiding cystourography were examined and enuresis was subtyped. Whole exome sequencing was performed in six individuals with familial segregation, the variants found in these individuals were screened in seven other individuals with PEN.

Results: In our family, PEN was inherited in an autosomal dominant pattern. Six individuals had PMEN, seven individuals had PNMEN. Bladder dysfunction was in three individuals, sleep disorder was in all individuals. Common variants were found in *PIGQ, CLCNKB, NCOR1, MROH2A, CCDC140* genes which may be candidates in the first group, only the c.568_571delinsTGAA (p.Arg190_Glu191delinsTer) variant in *NCOR1* gene was found to be heterozygous in other family members.

Conclusion: When the sociodemographic characteristics of the family were examined, bladder dysfunction and sleep disorder are the main predisposing factors for PEN. Familial PEN cases are rare and whole exome and genome studies to investigate the molecular basis of multifactorial diseases such as PEN are rarely performed. In order to clarify candidate genes in whole genome and exome studies of new PEN cases, it would be a more effective method to perform whole genome or exome studies on independent familial PEN cases.

Keywords: Familial, enuresis nocturna, whole exome sequencing, genetics, incontinence

ÖZ

Amaç: Enürezis nokturna çocukluk ve yetişkinlik döneminde yaşam kalitesini olumsuz etkileyen bir durumdur. Primer enürezis noktürn (PEN), beş yaşından sonra kuru bir dönem olmaksızın yatak ıslatmanın devam ettiği bir durumdur. PEN, alt üriner semptomlar eşlik ettiğinde PEN non-monosemptomatik (PNMEN), eşlik etmediğinde monosemptomatik (PMEN) olarak adlandırılmaktadır. PEN'in etiyolojisi üzerine yapılan çalışmalarda 4p, 8q, 12q, 13q, 22q kromozomal bölgeleri, *GNAZ, DRD5, D1B, NOS1, DRD4, PRDM13, SIM1, EDNRB, AQP2* genleri, rs9376454, rs60721117 varyantları genetik sorumlu olarak öne sürülmüştür. Burada PEN geniş bir ailenin sosyodemografik ve genetik bulguları incelenerek enürezis genetiğinin açıklığa kavuşturulması amaçlanmaktadır.

Gereç ve Yöntem: Ailenin ayrıntılı anamnezi alınmış, fiziksel muayeneleri, ultrasonografi ve voiding sistourografileri incelenmiş ve enürezisin alt tiplendirmesi yapılmıştır. Ailevi segregasyonu gösterilen altı bireyde tüm ekzom dizilemesi yapılmış ve bu bireylerde bulunan varyantlar ailenin PEN'li diğer yedi bireyinde taranmıştır.

Bulgular: Ailemizde tanısını koyduğumuz PEN'in, otozomal dominant geçişli bir durum olduğu, altı bireyin PMEN, yedi bireyin PNMEN ile uyumlu olduğu görülmüştür. Mesane disfonksiyonu üç kişide, uyku bozukluğu ise tüm kişilerde görülmüştür. Birinci grupta aday olabilecek

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ÖZ

PIGQ, CLCNKB, NCOR1, MROH2A, CCDC140 genlerinde ortak varyantlar saptanmış olup sadece *NCOR1* genindeki c.568_571delinsTGAA (p.Arg190_Glu191delinsTer) varyantı diğer aile bireylerinde heterozigot olarak bulunmuştur.

Sonuç: Sosyodemografik özelliklerine bakıldığında, PEN etiyolojisinde sorumlu bulunan mesane disfonksiyonu ve uyku bozukluğu ailedeki başlıca hazırlayıcı faktörledir. Ailesel PEN olguları nadirdir ve PEN gibi multifaktöriyel hastalıkların moleküler temelini araştırmak için tüm ekzom ve genom çalışmaları nadiren yapılmaktadır. Yeni PEN olgularının tüm genom ve ekzom çalışmalarında aday genleri netleştirmek için bağımsız ailesel PEN olgularında tüm genom veya ekzom çalışmaları yapmak daha etkili bir yöntem olacaktır.

Anahtar Kelimeler: Ailevi, enürezis noktürn, tüm ekzom dizileme, genetik, inkontinans

Introduction

The term "enuresis nocturna" denotes recurrent involuntary leakage of urine during sleep at least twice a week for at least three months in children older than five years of age without any organic cause according to International Children's Continence Society guidelines.[1] Enuresis nocturna is divided into primary and secondary subgroups. Primary enuresis nocturna (PEN) is defined as the continuation of urinary incontinence during sleep without a dry period, at the age of five years and above, when bladder control is expected to have developed without underlying lower urinary tract pathology,[2] accounts for 80-90% of all enuresis cases.[3] Enuresis is one of the most common childhood disorders, the worldwide prevalence of PEN ranges from 3.1 to 24.4%[4] and has been found to be 10.5-17.5% in Türkiye.[5]

Enuresis is more common in boys than girls in the early school years, the ratio of affected men and women is stated to be 17:22[6] and continues in adulthood with a rate of 2-3%.[7] PEN is divided into monosymptomatic (PMEN) and non-monosymptomatic (polysymptomatic) (PNMEN) subgroups. PMEN is a condition not accompanied by lower urinary tract pathology and symptoms.[8]

Although many experts have proposed many hypotheses about the causes of enuresis, the aetiology of enuresis nocturna has not been clearly clarified. According to Isola[9] when enuresis nocturna does not represent an epileptic attack, it corresponds to an pollution.

Since the 1950s, when enuresis was thought to be caused by the inability of the muscles to relax, there have been many views that enuretics have a smaller bladder capacity.[10] A molecular link has been demonstrated between the circadian rhythm gene *Per1* and *ENaC*, an epithelial sodium channel in the collecting duct, suggesting that circadian rhythm plays a direct role in diuresis and sodium retention.[11] Nevéus[12] examined the interconnections of three systems involved in urinary control, including nocturnal urine production, bladder storage ability, and arousal threshold.

In the genetics of enuresis nocturna, which has been investigated since 1930s, autosomal dominant inheritance model has been accepted rather than autosomal recessive inheritance model.[13-15] Twin studies gave equal results regarding inheritance from mother or father but; the risk of enuresis nocturna was found to be 3.63 times for maternal inheritance and 1.85 times for paternal inheritance.[16]

Eiberg et al.[6] showed a strong connection between PMEN and D13S291, D73S263 markers in the 13q13-q14.3 chromosome regions. Linkage studies showed the existence of a other locuses for PEN on chromosome 12q13-21[13] and 8q (D8S264).[17] In the study of von Gontard et al.,[18] it was found that 8q (D8S260, D8S257), 12q (D12S80, D12S43), 13q (D13S263, D13S291) chromosome regions were segregated together in families with enuresis. In the genome scanning analysis conducted by Eiberg[19] in 1998 on a family with primary nocturnal enuresis, the candidate region was detected on chromosome 22 (D22S446, D22S343 markers), and the *GNAZ* gene might be a candidate gene for PMEN. von Gontard et al.[20] investigated the linkage of nocturnal enuresis to a locus on chromosome 22 in thirty-five German families and showed that 39.3% of the families were compatible with markers on chromosome 22. In another linkage study by Eiberg et al.,[21] the 4p16.1 region and *DRD5, D1B* genes were thought to be candidate genes for enuresis. In the Loeys et al.'s[22] study on these three loci, thirty-two families with enuresis/incontinence were included, found linkage with chromosome 22q11 in nine families, 13q13-14 in six families and 12q in four families, but no evidence of chromosome 8q was detected. In a study conducted to previously identified loci, chromosomes 12 and 13 of four large families with ten individuals with nocturnal enuresis were genotyped, there was no evidence for linkage to two previously reported loci.[23] The frequency of the C allele in the *DRD4* promoter (-616; rs747302) was found significantly higher in PEN patients.[24] The children with enuresis, carrying the *C* allele in their *DRD4* promoter, had reduced gray matter volumes in their thalamus.[25] The genome-wide association study by Jørgensen et al.[26] identified two loci and risk genes associated with nocturnal enuresis, including *PRDM13, SIM1* and *EDNRB*, could affect sleep, urine production, bladder function, found a significant genetic overlap between nocturnal enuresis and attention deficit hyperactivity disorder, so they detected two candidate variants; rs9376454 (chromosome 6q16.2) and rs60721117 (chromosome 13q22.3) to be leading. A recent genetic study of treatment-resistant PEN cases, has drawn attention to the link between the *AQP2* gene and enuresis.[15]

In this study, it is aimed to elucidate the genetic mechanisms causing enuresis nocturna by genetic analysis of individuals with enuresis nocturna from a family with three generations of isolated enuresis nocturna cases.

Materials and Methods

The study included thirteen individuals with PEN from the same family who were referred to clarify their bedwetting history. When questioning the histories of enuresis nocturna,

the definition of enuresis nocturna in the International Cildren's Continens Society criteria was used.[1] It was learned that six members of the family were followed-up in urology and child psychiatry outpatient clinics. In the history of all symptomatic individuals, time of bedwetting during the day, age at onset and end of symptoms, frequency of wetting during the week and night, constipation, faecal incontinence, drinking water, frequency of urination, difficulty in urination, difficulty in urinary retention, frequency of daily voiding, presence of urinary flow disorder, depth of sleep and characteristics of sleep, history of birth trauma, allergy and parasitic diseases, history of head or pelvic trauma, history of urinary tract infection were questioned. Weight, height, external urinary system examinations were performed by physical examination and the results were recorded. Haemogram, biochemistry, complete urinalysis and urinary system ultrasonography were performed and signs of additional diseases were roughly excluded. Six individuals of the family who were followed up and treated were divided into Group 1 and the remaining seven individuals were divided into Group 2.

Whole exome sequencing (WES) allows the examination of all protein coding sequences (exons), some non-coding sequences (introns) and exon-intron junction regions of defined genes in the entire DNA sequence. When the exact disease-causing gene of a particular condition is not known, the examination of the entire DNA sequence is also used to search for candidate genes for the disease with the deductive method. For clarification of the genetic etiology of enuresis nocturna, venous blood samples of all individuals were collected in 4 mL ethylenediaminetetraacetic acid tubes in order to perform WES. DNA isolation was performed using QIAamp DNA Micro Kit[â]. Standard exome enrichment and library preparation of Group 1 were performed and the library was sequenced on the Illumina HiSeq 4000 with 2x150 bp paired-end sequencing at 50-100X target depth.

Statistical Analysis

All variants were mapped to the human reference genome hg19, those that passed the quality filters were checked on Integrative Genomics Viewer (IGV, https://igv.org/), then low frequency variants according to GnomAD v.4.1.0 (https://gnomad.broadinstitute.org/about) were analyzed using Microsoft Excel filtering. Pseudogenes were eliminated. In silico pathogenicity prediction tools and American Collage of Medical Genetics (ACMG) guidelines were used for variant selection. The variants obtained as a result of WES analysis of Group 1 individuals were filtered for the Human Phenotype Ontology (HPO) genes responsible for the mechanisms accused in the pathophysiology of enuresis nocturne. Rare variants with high pathogenicity and low community frequency detected in Group 1 were analysed in DNA samples isolated from Group 2 individuals by primer design [ENSEMBL-BLAST database (https://www.ensembl.org/Homo_sapiens/Tools/Blast) was used] in Mi-Seq Illumina Next Generation Sequencing device (Illumina Inc., San Diego, CA, USA).

Approval certificate dated 30.01.2019 and numbered 20.478.486 was obtained from Manisa Celal Bayar University Faculty of Medicine Health Board Ethics Committee for this study.

Results

Two brothers aged 11 and 14 years with enuresis nocturna and their father who had a history of enuresis in the past were consulted to the department of medical genetics and the pedigree of the family was initially analysed and thirteen individuals had a history of enuresis nocturna in the past. When the inheritance pattern in the pedigree was examined, it was learnt that there was no consanguineous marriage (or same village) between the parents of individuals with a history of enuresis nocturna. It was found that enuresis nocturna was inherited without skipping generations including the father of the proband, his father's siblings and his father's father. Since the ancestral individuals I-1, I-2, who are the ancestors of the inheritance, are currently not alive, no information about their enuresis nocturna history could be obtained. It was learnt that II-3, the mother of III-10 who had a history of enuresis nocturna, could not remember the history of enuresis nocturna. Looking at the general distribution of the pedigree, enuresis nocturna; is not inherited from a particular sex, but is passed on from both mother and father to their children, not inherited to a particular sex, but occurs in both boys and girls. The left part of the pedigree clearly shows vertical inheritance (no generation skipping). The affected male/female ratio was calculated as 8/5 (1.6). As detailed in Table 1, the age of onset of symptoms was questioned to differentiate primary and secondary enuresis nocturna and it was found that the symptoms of all family members continued from birth without a dry period and the mean age at the end was 9.7 years. The complaint of all members of the family is nocturnal, IV-6, IV-7 and III-14 individuals have intermittent daytime incontinence as well as enuresis nocturna. All members of the family have enuresis at least three nights a week. Bedwetting was observed at least one and at most three times in all members of the family on nights when enuresis was observed. None of the family members have complaints of drinking too much water or urinating frequently. Urinary retention manoeuvres (squatting/crossing) were observed in six individuals (IV-6, IV-7, III-10, IV-10, IV-11, III-14). Changes in walking were observed in two individuals (III-10 and IV-10). When the laboratory and imaging results were analysed, the urinary system ultrasonography of IV-11 showed Grade 1 ectasia of both renal pelvic-caliceal system and a post-mictional residual urine volume of 20 cc was measured in the urinary system ultrasonography of IV-6 individual. Among the three individuals whose bladder volume was measured by ultrasonography, the prevoid bladder volume of IV-7 individual was 144 cc (expected bladder volume according to Hjalmas formula was 360 cc) and the prevoid bladder volume of IV-12 individual was 50 cc (expected bladder volume according to Hjalmas formula was 300 cc).[27] All individuals described difficulty being awakened by high-frequency sounds and stimuli, but did not report any abnormalities in falling asleep and sleep duration (7-10 hours). Seven individuals described a

Table 1. Anamnesis findings of individuals

Symptoms	III-5	IV-6	IV-7	III-10	IV-10	IV-11	II-1	III-1	III-4	III-7	II-5	III-14	IV-12
Age (year)	42	14	11	48	20	17	75	50	45	40	61	37	13
Gender	Male	Male	Male	Female	Male	Female	Male	Male	Female	Male	Female	Male	Female
Time of bedwetting	Night	Night and day	Night and day	Night	Night	Night	Night	Night	Night	Night	Night	Night and day	Night
Start time	From birth	From birth	From birth	From birth	From birth	From birth	From birth	From birth	From birth	From birth	From birth	From birth	From birth
End time	7 years	Continuing	Continuing	9 years	9 years	8 years	10 years	8 years	8 years	8 years	11 years	13 years	11 years
Frequency of wetting (days/week)	3-4 nights/week	Every night	3-4 nights/ week	3-4 nights/ month	Every night	Every night	3 nights/ week	3-4 nights/ week	3 nights/ week	3-4 nights/ week	4-5 nights/ week	3-4 nights/ week	3-4 nights/week
Frequency of bed-wetting during the night	1 time	<3 times	<3 times	2 times	1 time	<3 times	1 time	1 time	1 time	1 time	1 time	1 time	<2 times
History of constipation	None	None	None	Yes	None	Yes	None	None	None	None	None	None	Yes
History of faecal incontinence	None	Yes	None	None	Yes	None	None	None	None	None	None	Yes	None
History of drinking too much water	None	None	None	None	None	None	None	None	None	None	None	None	None
Frequent urination	None	None	None	None	None	None	None	None	None	None	None	None	None
Daily frequency of urination	Every 3 hours	Every 2 hours	Every 2 hours	Every 2 hours	Every 2 hours	Every 3-4 hours	Every 2-3 hours	Every 3-4 hours	Every 2-3 hours	Every 2-3 hours	Every 2-3 hours	Every 2 hours	Every 2 hours
History of burning during urination	None	None	None	Yes	Yes	Yes	None	None	None	None	Yes	None	None
Urinary retention and/or difficulty while holding urine (squatting-crossing)	None	Yes	Yes	Yes	Yes	Yes	None	None	None	None	None	Yes (squatting)	None
History of urgent urination	None	Yes	None	Yes	None	Yes	None	None	None	None	None	None	Yes
Disturbance in urine flow	None	None	None	Yes (drop by drop)	None	Yes (discrete)	None	None	None	None	None	None	None
History of gait changes	None	None	None	Yes	Yes	None	None	None	None	None	None	None	None
Difficult awakening from sleep	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Snoring in sleep	None	None	None	Yes	None	None	None	None	None	None	None	None	Yes
History of sleep terrors	Yes	None	None	None	None	None	Yes	Yes	Yes	Yes	Yes	None	Yes
History of low birth weight	None	None	None	None	None	None	None	None	None	None	None	None	None
History of birth trauma	None	None	None	None	None	None	None	None	None	None	None	None	None
Food allergy	None	None	None	None	None	None	None	None	None	None	None	None	None
History of parasites	None	None	None	Yes	None	None	None	None	Yes	None	None	None	None
History of head trauma	None	None	None	None	None	None	None	None	None	None	None	None	None
History of pelvic trauma	None	None	None	None	None	None	None	None	None	None	None	None	None
History of recurrent urinary tract infection	None	None	None	None	None	Yes	None	None	None	None	None	None	None
History of recurrent urinary tract infection	None	None	None	None	None	None	None	None	None	None	None	None	None
Obesity	None	None	None	None	None	None	None	None	None	None	None	None	None
Treatments received	No treatment	Combined therapy	Combined therapy	No treatment	Combined therapy	Combined therapy	No treatment	No treatment	No treatment	No treatment	No treatment	No treatment	Regression with education and advice
History of psychosocial problems/psychological support	None	Yes	Yes	Yes	Yes	Yes	None	None	None	None	None	Yes	None
Socioeconomic and cultural level of the family	Low	Middle	Middle	Low	Middle	Middle	Low	Low	Low	Low	Low	Low	Middle
Behavioural disorder/attention deficit	None	None	Yes	None	Yes	None	None	None	None	None	None	None	None

history of sleep terrors (nightmare, fearful dream) (II-1, II-5, III-1, III-4, III-5, III-7, IV-12). None of the individuals had sleep apnoea. As shown on Figure 1 the findings of II-1, II-5, III-1, III-4, III-5, III-7 members of the family were compatible with PMEN; the findings of III-10, III-14, IV-6, IV-7, IV-10, IV-11 and IV-12 members were compatible with PNMEN.

Four members of the family received pharmacological and supportive treatments for enuresis nocturna. IV-6 was treated with desmopressin and reward therapy and it was observed that the number of wet nights in six months decreased from 56 to 2, after these treatments. IV-7 was treated with desmopressin and reward and punishment (restriction) therapies; it was observed that the number of wet nights in a month decreased from 28 to 2. IV-10 and IV-11 were treated with desmopressin and behavioural therapy together and benefited.

After anamnesis and detailed examination, genetic examination of blood samples was started. In each individual's exome data, firstly, exonic, exonic; splicing, intergenic, downstream, upstream, UTR3, UTR5, coding ribonucleic acid variants were selected in the functional reference gene filter. As a result of the analysis of six individuals who underwent WES variants with an allele fraction above 30%, read quality above 20% (exceeding 20X) in all individuals, considering the prevalence of enuresis nocturna, allele frequency below 18% were filtered. 15927 common variants in 9102 genes that met the ACMG criteria were obtained.

Based on the decreased prevoid bladder volume in two of the family members (IV-7,IV-12) and IV-6 individual's postmixed residual urine volume, the following findings related to overactive bladder in HPO; urinary urgency (HP:0000012), functional abnormality of the bladder (HP:0000009), urinary bladder sphincter dysfunction (HP:0002839), autonomic bladder dysfunction (HP:0005341), spastic/hyperactive bladder (HP:0005340), urinary incontinence (HP:0000020) subgroups, a total of 739 genes were filtered. Three common variants in *GALC, PIGQ*, and *CLCNKB* genes, not classified as benign/likely benign in the Clinvar database and with a gnomAD population frequency below 1% were found. As shown in Table 2, when the tissue expression distributions of the exons in which the variants were detected were analysed, it was observed that exon 17 in the *GALC* gene in which the variant was located was not expressed in any tissue. The exons of the variants in *CLCNKB* and *PIGQ* genes showed moderate expression in the renal medulla and cortex.

Based on the anamnesis of "deep sleep and difficulty in awakening" of all members and "sleep terror" of seven members, sleep disorders in HPO are defined as sleep-wake cycle disturbance (HP:0006979), disturbance during transitions between sleep and wake states (HP:5200293), sleep abnormality (HP: 0002360), abnormal sleep architecture (HP:5200298), sleep-wake inversion (HP:0031849), nocturnal seizures (HP:0031951), parasomnia (HP:0025234), hypersomnia (HP:0100786), sleep-wake cycle disturbance (HP:0006979), sleep terror (HP:0030765), somnambulism (HP:0025236) subgroups in total 747 genes were filtered, 4 missense rare variants were detected. As shown in Table 3, the exons of *SPIB* and *SIK1* variants were not expressed in brain, pituitary, kidney and bladder tissues in the pathogenesis axis of enuresis

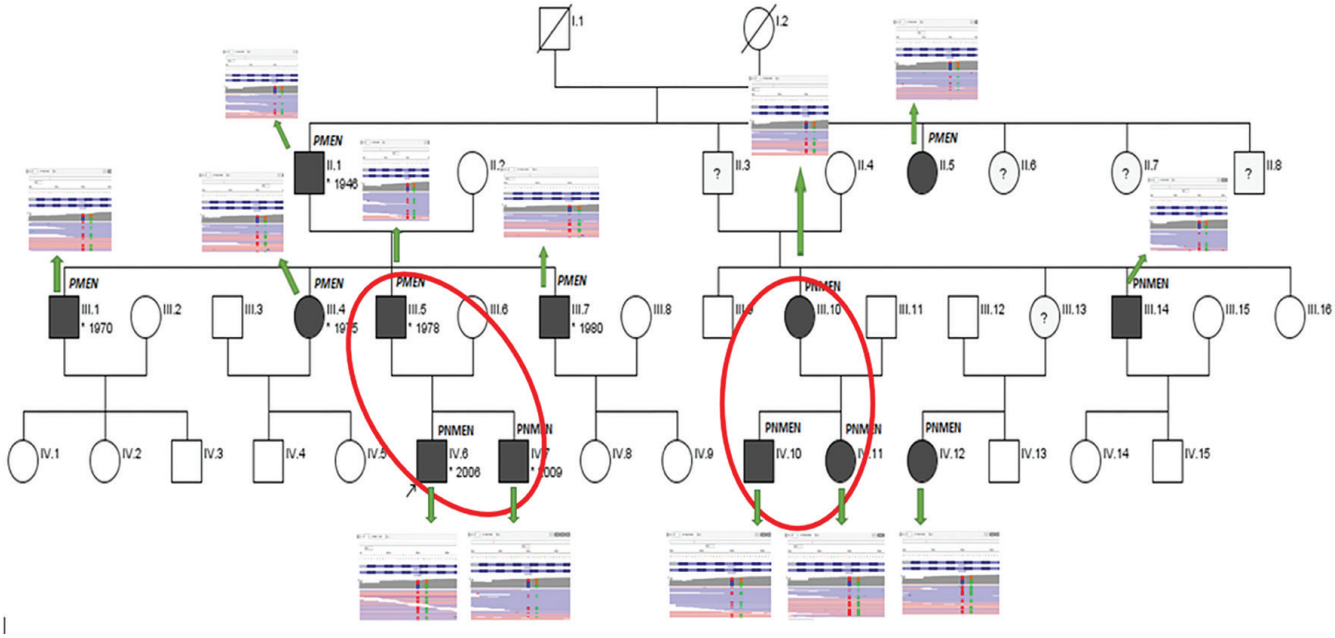

Figure 1. Representation of family aireys with PMEN and PNMEN on pedigree. II-5, IV-6, IV-7 and II-10, IV-10, IV-11 individuals were classified as Group 1 (red circled). The IGV image of the *NCOR1* c.568_571delinsTGAA variant detected in each individual is indicated by a green arrow on the pedigre

PMEN: Primary monosymptomatic enuresis nocturna, PNMEN: Primary non-monosymptomatic enuresis nocturna, IGV: Integrative Genomics Viewer

nocturna.

In the examination of the 8q, 12q and 13q chromosomal regions, which Eiberg et al.,[6] Arnell et al.,[13] Eiberg,[17] von Gontard et al.[18] and Loeys et al.[22] pointed out for enuresis nocturna in their studies, no variants that could pass the filters were found in these regions. 22q chromosomal region indicated by Eiberg[19] and von Gontard et al.[20] and Loeys et al.[22] *GNAZ* gene in the 22q11 region, pointed by Eiberg[19] were analyzed; all family members were homozygous for the *SCARF2* c.2232delinsGG frameshift variant (22q11.21), whose allele frequency was not found in any pupulation, not included in Clinvar, Likely Patogenic (PM2, PVS1) according to ACMG evaluation, but reputable source recently reports it as benign (BP6). In the examination of 4p chromosome region and *DRD5*, *D1B* genes pointed out by Eiberg et al.,[21] no common rare variant found. No genetic change found in the *DRD4* gene, chr11:636689 locus which Dai et al.[24] emphasized but chr11:637578 G>C benign change found to be heterozygous in three family members (III-10, IV-10, IV-11). Among the risk genes *PRDM13, SIM1* and *EDNRB* that Jørgensen et al.[26] pointed out in their genome-wide association study on enuresis, no variant that could pass the filters was detected. Neither of the two variants of rs9376454, rs60721117 (on chromosome 6q16.2, chromosome 13q22.3) was found none of the individuals. All family members were heterozygous for an intronic variant (c.3600+62del-rs200671404), in the epithelial sodium channel-associated circadian rhythm gene *PER1* that is not located in an intronic non-coding splice site and is not predicted to be the result of a splice modifier (BP7). The *AQP2* c.295 G>A variant of uncertain significance variant, which was detected in one individual (IV-7), was not found in the family in this study and six benign variants of the *AQP2* were homozygous in some individuals and heterozygous in some individuals and the population frequencies of these variants were very high (48-68%).

In the overall analysis, three variants with high pathogenicity common to all family members were remarkable (Table 4). It was observed that these three variants in *NCOR1, MROH2A* and *CCDC140* genes had not been detected previously in population frequency studies. Due to the high variant pathogenicity scores according to ACMG, these variants were included in the next

Table 2. Tissue expression levels of exons of variants associated with overactive bladder and decreased bladder capacity in the Gtex portal

Variant name	Min-max fraction in family	Function	Allele frequency (gnomAD v.4.1.0)	ACMG value	Tissue expression
GALC c.1834+5_1834+9delinsGTGACT (ENST00000261304.7) (Exon17)	0.46-0.73	Splice region	Not found in any population	PM2	No expression*
***PIGQ* c.2002_2003inv (p.Cys668His) (ENST00000026218.5) (Exon 10)**	0.46-1.00	Missense	Not found in any population	PM2	Kidney medulla (MRCPB 2.97)
***CLCNKB* c.641_642delinsGC (p.Ala214Gly) (ENST00000375679.4) (Exon 17)**	1.00-1.00	Missense	Not found in any population	PM2	Kidney medulla, (MRCPB 6.26) Kidney cortex (MRCPB 5.66)

*Exon 17 is not expressed in any tissue, MRCPB: Median read count per base, PM2: Pathogenic moderate-2, ACMG: American Collage of Medical Genetics

Table 3. Tissue expression of exons of variants associated with sleep disorders in Gtex portal

Variant name	Min-max fraction in family	Function	Allele frequency (gnomAD v.4.1.0)	ACMG value	Tissue expression
***PIGQ* c.2002_2003inv (p.Cys668His) (ENST00000026218.5) (Exon 10)**	**0.46-1.00**	**Missense**	**Not found in any population**	**PM2**	**Kidney medulla (MRCPB 2.97)**
SPIB c.309_310delinsCC (p.Ala104Pro) (ENST00000595883.1) (Exon 4)	0.39-1.00	Missense	Not found in any population	PM2	No expression**
***CLCNKB* c.641_642delinsGC (p.Ala214Gly) (ENST00000375679.4) (Exon 7)**	**1.00-1.00**	**Missense**	**Not found in any population**	**PM2**	**Kidney medulla, (MRCPB 6.26) Kidney cortex (MRCPB 5.66)**
SIK1 c.1844_1848delinsTCCCT (p.Ala615Val) (ENST00000270162.6) (Exon 13)	1.00-1.00	Missense	Not found in any population	PM2	No expression***

Only-EBV-transformed lymphocytes, spleen, terminal ileum and transverse colon expression,*There is no expression of exons other than exon 15, MRCPB: Median read count per base, PM2: Pathogenic moderate-2, ACMG: American Collage of Medical Genetics

Group 2 study step (Table 4).

Variants in *GALC, SPIB* and *SIK1* genes (exon 17, exon 4 and exon 13), which were found to be mechanism-related in Group 1 analyses, were not included in the Group 2 study because they were not expressed in any tissue according to the Gtex portal. Variants detected in *PIGQ, CLCNKB, NCOR1, MROH2A, CCDC140* genes were analysed in seven individuals in Group 2. Among the variants screened, only the *NCOR1* c.568_571delinsTGAA variant was found to be heterozygous in all family members (Table 5). The variant was read both forward and reverse in the next generation sequencing analysis of all family members as shown in Figures 1 and 2 and its allelic fraction was determined to be 45-53% in all family members, indicating that the variant is inherited heterozygously (Table 5).

Discussion

The most important factor suggesting that enuresis is genetic is the prevalence of family history. Many studies report that approximately half of enuretic children have parents who also experienced this condition. Specific data show that 57% of children with enuresis have parents with the condition, with this rate distributed as 58% in fathers, 36% in mothers, and 6% in both; the presence of this condition in the father is also associated with a high probability ratio of ~5.7.[28] In this study, which aims to investigate genetic factors in the etiology of enuresis, a large family of thirteen cases of PEN from three generations was analysed sociodemographically and genetically. The fact that enuresis does not skip generations in this family in which there is no consanguineous marriage and is transmitted from both mother and father to both girls and boys regardless of gender shows that it is inherited by autosomal dominant inheritance.[12,29] In the first stage of the study, genetic changes in the chromosomal regions 8q,[17] 6q16,[26] 12q,[13] 13q,[6] 4p,[21] and 22q,[19] which were previously predicted to be associated with enuresis, were filtered for common variants among all individuals, and no common, rare, and disease-related variant was found. Although the coverage of the *PRDM13, SIM1,*

Table 4. Allele frequency and functions of the three variants with the highest pathogenicity according to ACMG criteria

Variant name	Min-max fraction in family	Function	Allele frequency (gnomAD v.4.1.0)	ACMG value	Tissue expression
NCOR1 c.568_571delinsTGAA (p.Arg190_Glu191delinsTer) (ENST00000268712.3) (Exon 5)	0.26-0.48	Nonsense	Not found in any population	Likely pathogenic (PVS1, PM2)	Brain, hypothalamus (MRCP 0.138) Kidney medulla, (MRCPB 0.261) Bladder (MRCPB 0.233)
MROH2A c.2336T>C (p. Leu779Pro) (NM_001367507.1) (Exon22)	0.47-0.60	Missense	Not found in any population	VUS (PM2)	**Kidney cortex (MRCPB 0.006)**
CCDC140 c.250G>T (p.Gly84Ter) (ENST00000295226.1) (Exon 2)	0.39-0.58	Stop gained	Not found in any population	VUS (PM2)	No expression****

****There is no expression of exons other than exon 3, VUS: Variant of uncertain significance, PM2: Pathogenic moderate-2 (extremely low frequency in gnomAD population databases), PVS1: Patogenic very strong-1 (null variant in a gene where loss of function is a known mechanism of disease), ACMG: American Collage of Medical Genetics

Table 5. Zygosity status of five variants obtained from whole exome sequencing analysis of Group 1 individuals in Group 2 individuals

Variation	Indivisual						
	II-1	**II-5**	**III-1**	**III-4**	**III-7**	**III-14**	**IV-12**
PIGQ c.2002_2003inv (p.Cys668His) (ENST00000026218.5) (Exon 10)	Het	-	Het	-	Hom	-	Het
CLCNKB c.641_642delinsGC (p.Ala214Gly) (ENST00000375679.4) (Exon 7)	-	Het	Hom	Hom	-	Hom	Het
NCOR1 c.568_571delinsTGAA (p.Arg190_Glu191delinsTer) (NM_006311.4) (Exon 5)	**Het**	**Het**	**Het**	**Het**	**Het**	**Het**	**Het**
MROH2A c.2336T>C (p. Leu779Pro) (NM_001367507.1) (Exon22)	Het	Het	-	-	-	-	-
CCDC140 c.250G>T (p.Gly84Ter) (ENST00000295226.1) (Exon 2)	Het	Het	-	-	-	Het	-

Het: Heterozygous, Hom: Homozygous

EDNRB, PER1, and *AQP2* risk genes was complete, no candidate variants were found in any of them.

Many theories have been put forward since the 1960s that children with enuresis have small bladder volumes. So far, the general opinion on this subject is that nocturnal detrusor overactivity may be effective in enuretic children.[30,31] Bladder dysfunction was detected in three members of the family (IV-7,IV-12,IV-6) and this finding guided the clinical filtering of WES variants. All individuals stated that they had difficulty waking-up from sleep and they were awakened by loud noises or physical stimuli. Some individuals reported that they had fearful dreams and woke up with a distinct scream, and some individuals reported snoring during sleep.

This family situation supports reports in the literature showing that children with enuresis nocturna suffer from uncomfortable sleep.[32,33] In a recent study analysing the global prevalence of enuresis nocturna, it was reported that it was more frequent in patients with low socioeconomic status and positive family history.[34] The three generations of vertical transmission and the middle-low income level in this family we analysed support this information. In this context, it was aimed to analyse the common genetic changes in the largest family that could be found by WES method. All exon sequences and intronic regions were analysed and candidate variants of the family with were considered in the first stage. Three common variants in the *GALC, PIGQ* and *CLCNKB* genes were identified through filtering of genes associated with urinary retention, bladder dysfunction, urinary bladder sphincter dysfunction, autonomic bladder dysfunction, spastic/overactive bladder, and urinary incontinence in HPO. Based on the finding that deep sleep and sleep terror symptoms in family members suggest a connection between enuresis and deep sleep, sleep disorders in HPO include sleep-wake cycle disorder, impaired transitions between sleep and wakefulness states, abnormal sleep architecture, sleep-wake reversal, nighttime seizures, parasomnia, hypersomnia, sleep-wake cycle disorder, sleep terror, and somnambulism. Four missense variants were detected in the *SPIB, SIK1, PIGQ* and *CLCNKB* genes. But three of variants (in the *GALC, SPIB* and *SIK1* genes) were found not to show appropriate tissue expression. The presence of two variants in the two genes *PIGQ* and *CLCNKB*, which are associated with the responsible mechanism, was promising. Group 2 included variants in the *NCOR1, MROH2A,* and *CCDC140* genes, as well as variants in the *PIGQ* and *CLCNKB* genes identified through mechanism filtering. Only the variant in the *NCOR1* gene was found to be heterozygous (allele frequency: 45-53%) in Group 2 individuals. This loss-of-function variant was not found in the gnomAD v.4.1.0 population screen. It was evaluated as PVS1 and PM2 according to in silico prediction tools. Brain and bladder expression of the 5th exon in which the variant is located was found to be expressed in the bladder, brain and hypothalamus. The probability to autosomal dominant score of the gene was 0.9992, indicating a very highly dominant effect. *NCOR1* gene, encodes a transcriptional choregulatory protein involved in the balance between histone acetyltransferases and histone deacetyltransferases. *NCOR1* loss-of-function intolerant (pLI) score of 1.00 indicates that it is a dosage-sensitive gene and the role of truncating mutations in autism spectrum disorder and intellectual disability has been shown.[35,36] The fact that enuresis nocturne is observed more frequently in children with autism spectrum disorder is frequently included in current studies.[37,38]

NCOR1 protein is 2440 amino acids long and has G-protein pathway suppressor 2-interacting and Myb-like DNA-binding functional domains between amino acids 150-238 and 627-670, respectively.[39] *NCOR1* c.568_571delinsTGAA p.(Arg190_Glu191delinsTer) mutation results in a prematurely terminated stubby protein and causes loss of functional domains. As seen in Figure 3, while the wild type (Red) protein has 1 alpha helix structure in the first 190 amino acids, the mutant type (Blue) stubby protein formed as a result of the mutation is predicted to have more alpha helix structures using protein folding models. As a result of the loss of functional regions of the protein and

Figure 2. IGV image of the NCOR1 c.568_571delinsTGAA variant
IGV: Integrative Genomics Viewer

changes in the folding model, it is predicted that this mutation will cause the protein to lose its function. Exon 5 in which the variant is found is expressed in tissues in the pathogenesis pathway of enuresis nocturna,[40] albeit at a low level (Table 4).

The variant screening phase in Group 2 individuals was also performed using the new generation sequencing (Mi-Seq Illumina) method. Since it was not possible to reach the families for new sample collection, confirmation with Sanger could not be performed. The IGV readings of the c.568_571delinsTGAA (p.Arg190_Glu191delinsTer) variant in *NCOR1* gene detected in the family were shown on the pedigree (Figure 1). In the functional analysis of the variant, it was concluded that it changes the protein structure and the exon in which it is located is expressed in the bladder, brain, hypothalamus which have main roles of sleep pathways and enuresis. *NCOR1* forms complexes with many other proteins responsible for neural development. This indirectly suggests that this protein plays an important role in neural development. Heterozygous mutations in the *NCOR1* gene are predicted to be a cause of syndromic intellectual disability/autism spectrum disorder together with neural development proteins.[40]

The family we studied with nocturnal enuresis confirms the mechanisms of nocturnal enuresis with its sociodemographic and genetic characteristics. In short, the fact that nocturnal enuresis does not skip generations and is passed on to both daughters and sons from both the mother and father strongly suggests that the condition is transmitted through autosomal dominant inheritance. The presence of both bladder symptoms and difficulty waking up from sleep in the family history reflects the general history of individuals with nocturnal enuresis in our society and reiterates the need to focus more on these mechanisms.

When considering the etiology of nocturnal enuresis from a broad perspective, the most recent review concluded that familial background is a factor, but a single Mendelian inheritance pattern has not yet been identified, and the matter remains open-ended.[41] The research clearly shows that nocturnal enuresis is caused by genetic factors, but we have found that WES alone may be insufficient in this regard, and that studies need to be conducted with additional tests in larger independent groups. The *NCOR1* gene has opened the door to the possibility that enuresis may result from the immaturation of neurodevelopmental processes, and meaningful changes in this gene could be included in functional studies in future research on this topic.

Study Limitations

The *NCOR1* c.568_571delinsTGAA p.(Arg190_Glu191delinsTer) variant has not been demonstrated in any healthy population in the gnomAD v.4.1.0 (Fraction of individuals with coverage over 30 is 0.7) and the possibility of missing coverage in this range is a disadvantage. Even with good whole exome coverage, the possibility of missing a variant that may be very rare in family members should also be considered. All genetic studies conducted on the family we worked with were performed using next-generation sequencing. One limitation of the study is that confirmation could not be obtained using Sanger sequencing, as it was not possible to contact family members to obtain new samples for confirmation.

A limitation of the study is that whole exome/whole genome sequencing could not be performed on all family members, including individuals without symptoms, and the variant found could not be shown to be absent in healthy individuals. Since enuresis nocturna is a questioning based on the past, there may be error rates due to failure to recall in such voluntary studies. Polymorphic variants predisposing to multifactorial diseases such as enuresis nocturna are known to cause disease together with facilitating factors. In this context, it is more likely to be a polymorphic change that produces a founder effect rather than a rare pathogenic/likely pathogenic change of a single gene.

Bladder symptoms in the family have been recorded in some individuals using voiding cystourethrography, but sleep symptoms are based solely on findings from the medical history and observations and have not been confirmed by a sleep laboratory or sleep electroencephalography. Although

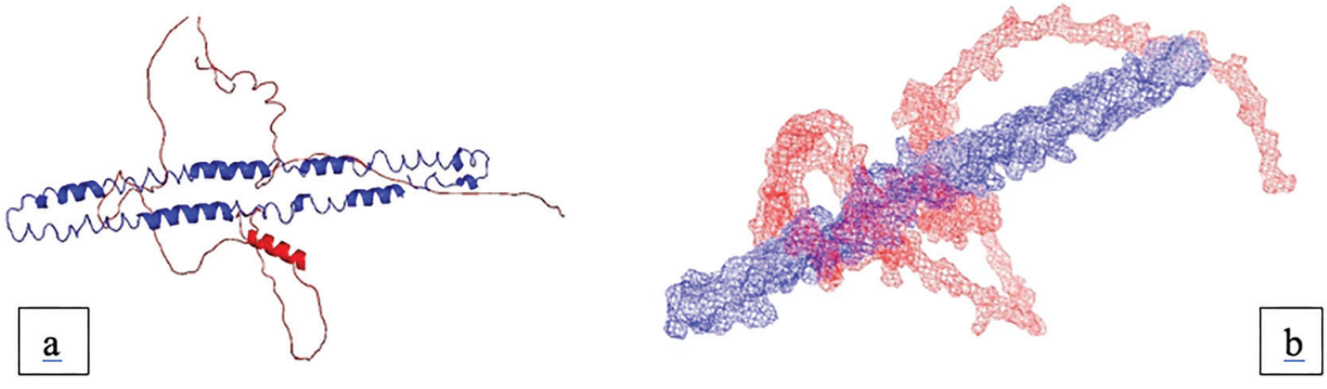

Figure 3. Protein modelling of the *NCOR1* c.568_571delinsTGAA variant was performed in I-TASSER v.5.1 (a) and PyMol V.2.5.5 analysis programs (b). The wild-type (Red) protein has one alpha-helical structure, while the mutant type (Blue) protein, which is formed as a result of mutation, exhibits more alpha-helical structures

most studies conducted to date have strongly emphasized the connection between enuresis and sleep depth, the observations of the parents of the subjects in these studies have been considered a strong finding.[42-45]

Conclusion

Genetic studies in our country are still lacking, both due to the inadequacy of our healthy population studies and for cost reasons. One reason why the underlying causes of conditions such as enuresis, which negatively affect the mental health of children and adolescents, cannot be clarified is the difficulty of conducting high-cost studies such as genetic studies in our society. This study is the first genetic study in the world conducted on a family with three generations of nocturnal enuresis and is unique in the literature.

Ethics

Ethic Committee Approval: Approval certificate dated 30.01.2019 and numbered 20.478.486 was obtained from Manisa Celal Bayar University Faculty of Medicine Health Board ethics committee for this study.

Informed Consent: Written informed consent was obtained from all parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.S.Ç., Concept: A.A.G., F.S.Ç., Design: A.A.G., F.S.Ç., Data Collection or Processing: A.A.G., Analysis or Interpretation: A.A.G., Literature Search: A.A.G., F.S.Ç., Writing: A.A.G., F.S.Ç.

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