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The Connection between Neuroblastoma Amplified Sequence Gene (NBAS) and the Short Stature-Optic-Atrophy-Pelger-Huet Anomaly Syndrome (SOPH) Literature Review

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Abstract

Background.
Clinical and natural heterogeneity is the main characteristic of inherited multisystem conditions with severe growth restriction. Nonetheless, the source of the originof these diseases are not completely investigated. Afore-mentioned afflictions are widespread among the population of Yakuts, located in the Republic of Sakha, which belongs to Russian Federation. Among the Yakuts, these conditions remarked by acute postnatal development hindrance, brachydactyly, optic atrophy (impairment of visual acuteness and color reflection), Pelger-Huet incongruity of WBCs and craniofacial dysmorphism but with average level of intelligence (1). Other features encompass chronic liver failure, underdeveloped cheekbones, loose skin, skeletal deformities and diminished tissue turgor (2).
Purpose of Study.
The overall objective of this research paper is to locate the gene that causes SOPH disorder.
Methods
The study uses secondary data from scientific journals published in authoritative databases, PubMed indexed in this case. The journal articles provide scientific investigations and information about the SOPH disease, NBAS gene and other relevant themes. A population sample of 129 individuals from five published research journals was considered.
Results
All reviewed researches were coherent in connecting SOPH syndrome with NBAS gene mutations.
Conclusion
Biological pathogen of the SOPH syndrome is NBAS gene.

Keywords*: SOPH syndrome, NBAS gene, optic atrophy, PHA, mutation, short stature, ALF, and phenotype.*

Abbreviations.
1. SOPH- Short stature-optic atrophy-pelger-huët anomaly
2. NBAS- Neuroblastoma amplified sequence
3. WBC-White blood cells.
4. CUL7- Cullin 7
5. DDX1-Amplification of a DEAD box gene
6. ILFS2- Infantile liver failure syndrome 2
7. DOA- Dominant Optic Atrophy
8. PHA-Pelger-Huet anomaly
9. LBR- Lamin B Receptor
10. SD-Standard deviation
11. ALF-acute liver failure
12. PHA- Pelger-Huet Anomaly
13. PID-Primary immunodeficiency

I. INTRODUCTION

Short stature disorders are clinically and genetically heterogeneous and demonstrate deceleration in growth and dysmorphism of the face and body. Whereas a number of genes are linked with hereditary short stature syndromes, only a few explanation is available. The Yakuts, who dwell in the Sakha Republic of Russian Federation, are distinguished as the population with a predomination of SOPH disorder. (3-4) Short stature syndrome is an infrequent phenomenon in the general population, but for the Yakuts, it is an important and prevailing condition (5) among other inherited diseases. The researchers have found that Yakut population is familiar with

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two kinds of short stature syndromes. Yakut patients exhibitdefects in CUL7gene, which is a triggering factor of the 3-M syndrome, leading to pre and postnatal development impedance and dysmorphic features of face. (6) Yakuts are also vulnerable to another, slightly different type of short stature syndrome. The latter represents autosomal recessive inherited disease, characterized by postnatal growth retardation, PelgereHuët abnormality and the loss of visual acuteness. (1) NBAS gene is responsible for the two clinical scenarios. The first one is the Short stature with SOPH and optic nerve atrophy, the second is known as ILFS2. (7) Dominant Optic Atrophy (DOA) is a type of neuro-ophthalmic disorder that is expressed in bilateral degeneration leading to insidious visual loss. The retinal ganglion cells' damage impedes the transfer of visual data between the photoreceptors and the lateral geniculus of the brain. DOA belongs to the group of innate optic neuropathies. (8) Pelger-Huet anomaly (PHA) is a genetic blood disease that makes the nucleus of white blood cells dumbbell, peanut-shaped or bilobed. The majority of PHA patients are asymptomatic and do not subordinate the treatment. (9) The trigger of the PHA is the deviation of the LBR gene. The mutation takes place in band 1q42. (10) The vacillation in the NBAS gene in the COOH-terminus is the cause of SOPH. (11)

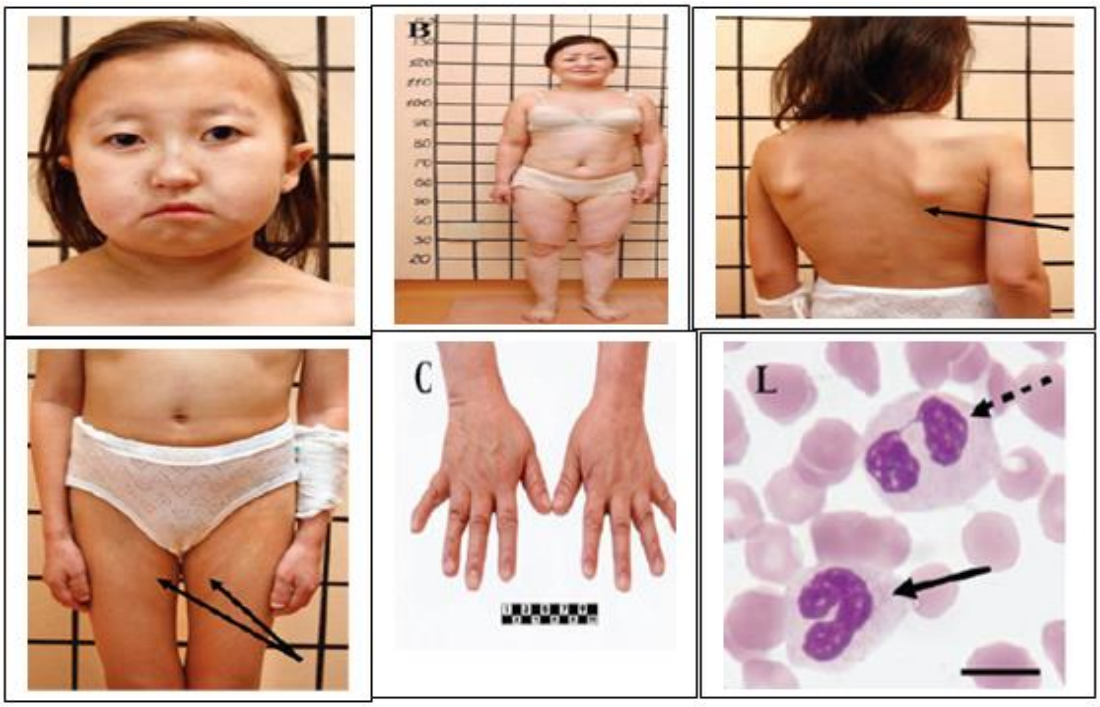

Fig: 1-Clinical features of patients with SOPH (1)

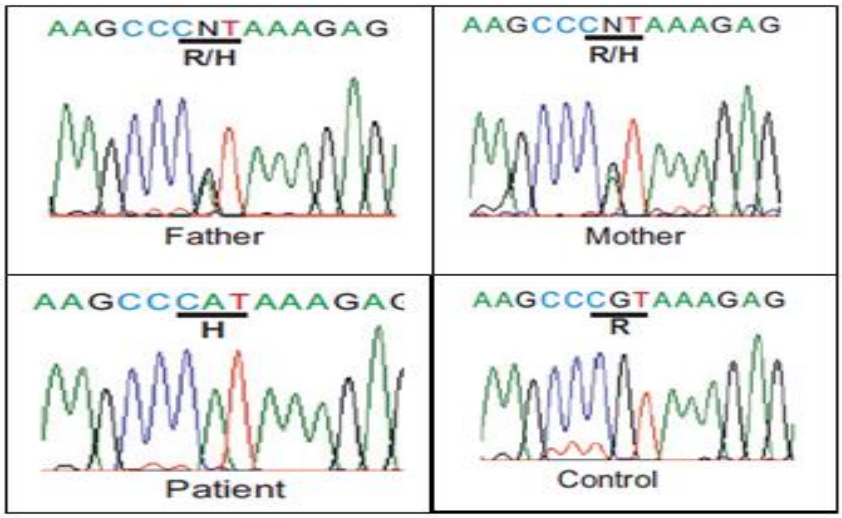

Figure 2: Neuroblastoma amplified sequence (1)

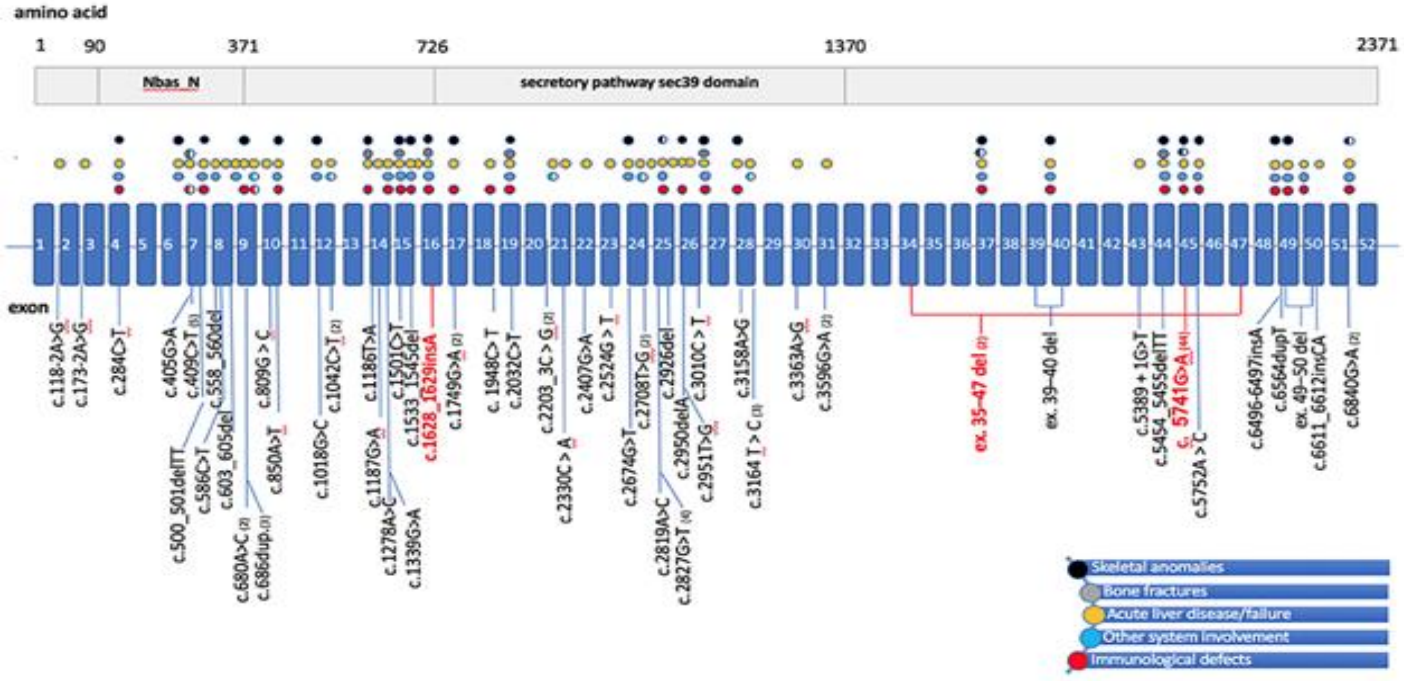

Fig: 3- NBAS mutations (31)

II. RESULTS

➢ *The First Research Journal*

The first scientific research paper is published by the US National Library of Medicine National Centre of Biotechnology Information. The objective of the research was to determine the gene that was the source of SOPH. Thirty-one Yakut families were recruited. The main characteristics for the inclusion criteria were low height compared to their age class, optic atrophy and autosomal receding inheritance. The ophthalmological assessment was conducted, patients with CUL7 mutation were separated, and ordinary people were enlisted in the research for the control experiment. Genome wide and fine homozygosity mapping of the autosomes by microsatellite markers, immunohistochemical analysis and mutational analysis for DDX1 and NBAS genes were conducted.

➢ *Clinical features of short stature disorder*

There were twenty-two female and twelve male patients, and the average standard deviation of their heights at birth was -0.94±0.29 and 0.31±0.42, respectively. After one year, the standard deviation of their heights were -4.44±1.19 and -3.16±1.06. It is observed that growth retardation is more severe in females than males, and no significant changes were detected between the ages. All of the patients had an average level of intelligence except for one subject. 88% of participants had a flat occipital area and brachycephalic skull. The patients had straight noses, small orbital cavities, underdeveloped cheekbones, long philtrum and thin lips. Further observations included the decreased skin elasticity and tissue turgor, shorter limbs relative to the body length, smaller feet and hands, brachydactyly was apparent in all patients. In addition, latebone aging of the hands, ossification of the vertebral apophysis, spine changes and hypoplasia were oberved in some cases. Hypolobulation of granulocyte nuclei was evident in all subjects of research. (1)

➢ *Identifying NBAS gene in SOPH disorder*

NBASand DDX1 genes were recognized in critical region. Researchers deployed the cycles of intronic primers and amplified the codes of exon-intronic intersections in order to have sequantially analyzed both genes. The alterations were not detected in DDX1, however, all patients except for one had altered nucleotides in thehomozygous mode of NBAS gene. The research concluded that NBAS gene is connected to SOPH syndrome. (1)

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	Frequency; numbers of patients who had each clinical feature (percentage)		
	Sex		
	Women	Men	Total
Number of patients	22	12	34
Constitution			
Normal length at birth	11 (50)	9 (75)	20 (58)
Postnatal growth failure	22 (100)	12 (100)	34 (100)
Craniofacial features			
Brachycephalic skull	20 (90.9)	10 (83.3)	30 (88.2)
Hypoplasia of frontal and parietal tubers	20 (90.9)	11 (92)	31 (91.2)
Narrow forehead	20 (90.9)	11 (91.7)	31 (91.2)
Long senile face	21 (95.4)	12 (100)	33 (97.1)
Small features of face	19 (86.4)	10 (83.3)	29 (85.3)
Facial asymmetry	19 (86.4)	5 (41.7)	24 (70.6)
Straight nose with prominent glabella	19 (86.4)	12 (100)	31 (91.2)
Thick/bushy eyebrows	15 (68.2)	9 (75)	24 (70.6)
Small orbit	22 (100)	11 (91.7)	33 (97.1)
Bilateral exophthalmos	20 (90.9)	11 (91.7)	31 (91.2)
Hypertelorism	3 (13.6)	2 (16.7)	5 (14.7)
Epicanthus	16 (72.7)	6 (50)	22 (64.7)
Hypoplastic cheekbone	21 (95.4)	12 (100)	33 (97.1)
Long philtrum	19 (86.4)	9 (75.0)	28 (82.4)
Thin lips	20 (90.9)	8 (66.7)	28 (82.4)
Body and extremity features			
Short neck	19 (86.4)	11 (91.7)	30 (88.2)
Loose and senile skin	22 (100)	12 (100)	34 (100)
Depressed turgor of tissue	22 (100)	12 (100)	34 (100)
Fine hair	17 (77.3)	8 (66.7)	25 (73.5)
Hypermobility of small joints	20 (90.9)	10 (83.3)	30 (88.2)
Muscular hypotonia	18 (81.8)	10 (83.3)	28 (82.4)
Micromelia	22 (100)	12 (100)	34 (100)
Brachydactyly	22 (100)	12 (100)	34 (100)
Syndactyly	1 (4.6)	1 (8.3)	2 (5.9)
Simian crease	3 (13.6)	2 (16.7)	5 (14.7)
Wide feet with high arch	19 (86.4)	11 (91.7)	30 (88.2)
Sandal chink	18 (81.8)	8 (66.7)	26 (76.5)
Wide big toe	18 (81.8)	8 (66.7)	26 (76.5)
Ophthalmological findings			
Bilateral optic nerve atrophy	22 (100)	12 (100)	34 (100)
Strabismus	6 (27.2)	3 (25.0)	9 (26.5)
Pigmented nevus	1 (4.6)	1 (8.3)	2 (5.9)
Myopia	9 (40.9)	3 (25.0)	12 (35.3)
Hypermetropia	1 (4.6)	2 (16.7)	3 (8.8)
Radiological findings			
Delay of chronological age	7 (31.8)	7 (58.3)	14 (41.2)
Neurological findings			
Normal intellectual function	21 (95.5)	12 (100)	33 (97.1)
Pathology of other systems			
High voice with harsh timber	21 (95.5)	11 (91.7)	32 (94.1)
Hypoplasia of uterus	4 (18.2)	0	4 (11.8)
Insulin dependent diabetes	2 (9.1)	0	2 (5.9)
Hypoplasia of thyroid gland	2 (9.1)	1 (8.3)	3 (8.8)

Table 1: clinical features in 34 Yakut patients (1)

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➢ *The Second Research Journal.*

The second research journal can be found in PubMed database. It analyzes, reports and investigates the state ofa 3 year old boy, with medical features, such asrecurrent acute liver failure (ALF) and numerous defects in NBAS gene. The samples were also taken from his younger brother and parents, therefore, research included 4 individuals. Whole-genome sequencing, Sanger sequencing, western blot analysis and in silico analysis were conducted. (12)

The boy was born after the 7 month of pregnancy. The weight of the new-born was 1512 g (-2.3 SD) and height equald to 42.5 cm (−0.8 SD).After the three years from birth, radiographs exposed retarded bone maturation. When boy was 7 years old, short stature became evident: −2.4 SDs in height. It was affirmed that the family had no records of liver disease. In the period of three years, theboy had developed the upper respirational tract infection, high liver enzyme intensities and jaundice. (12)

After the second acute liver failure, a liver wedge biopsy exposed an irregular surface and yellowish look. (Fig.4b). The Histopathology of hepatocytes was unevenly decayed, Showed cytoplasmic vacoulation and moderate macrovesicular steatosis. Apart from that, an augmentation of resident immunecells (CD8+ Tnamely) were obvious in the portal area. (Fig. 4c). Bile plug formation and various microvesicular lipid drops were also detected. (Fig. 4d). During the visualization of reticular fiber nominal bridging fibrosis were noticed (Fig. 4e). (12)

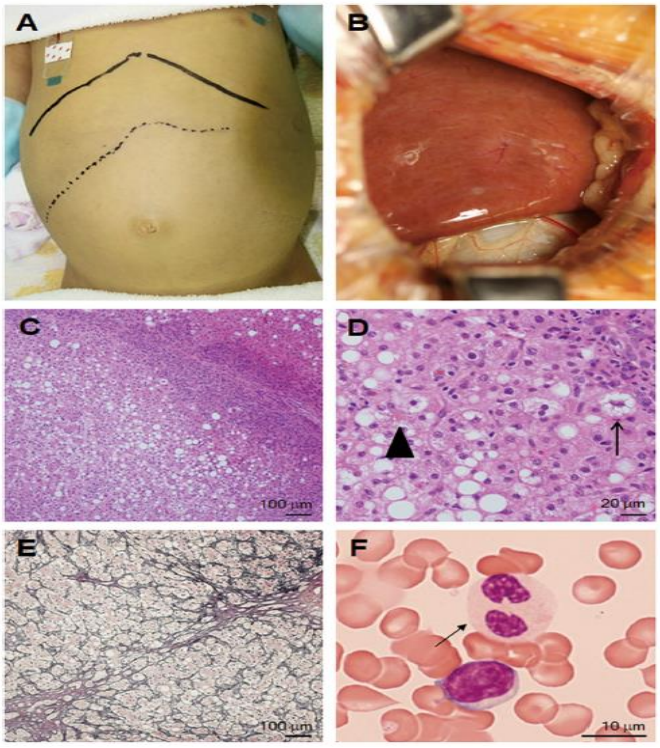

Figure 4 (12)

In spite of the fact, that NBAS gene alterations do not commonly display a liver phenotype, it is still noticed in SOPH disorder patients. (13) Haack et al. (14) identifiedcompound heterozygous and homozygousNBAS gene mutations in recurrent ALF patients. The given research alongside with other discussed research projects showed that the patients expose SOPH and ALF if they have homozygous and compound heterozygous NBAS gene mutations(13-14). According to the results of this research, the main agent of SOPH is NBAS gene.

➢ *The Third Research Journal.*

A Journal article published by PubMed and the European Journal of Ophthalmology represents a case report about NBAS mutations in SOPH. The case involves a 5-year-old girl having mental delay, high myopia, and strabismus. A funduscopic examination wasimplemented. The patient was found to have optic atrophy, which was manifestedthrough the slim thinned arteriol cavities and bright brown reflex central retina. (15)

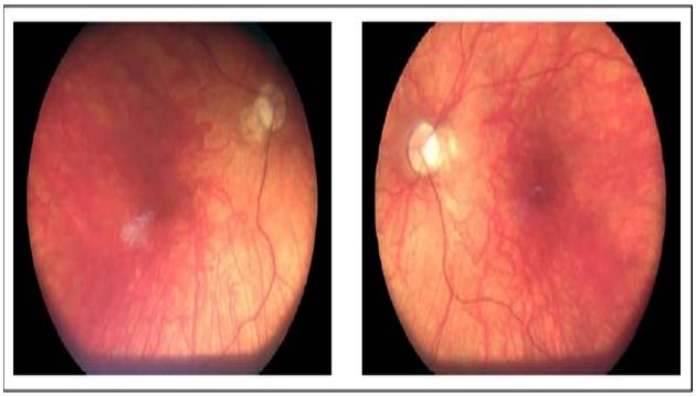

Fig: 5-Funduscopic features: brownish central retina with thinning arterioles in the optic disk. (15)

The child had fixed convergent strabismus towards the right eye. Apart from that, impaired ocular abduction and nystagmuswere detected. Acute pathologic myopia, optic atrophy and diffuse retinal depigmentationwere also apparent.When the patient was transported to the laboratory, she tested positive for severe liver disease too. Later, NBAS-SOPH like alteration was confirmed after a few months. A further examination revealed that her growth retardation included dental and skeletal development. (15)

The role of the CUL7 gene was also researched and connected with the 3-M syndrome. 3-M syndromy is an infrequent disease which leads to pre and postnatal growth impedance, average intelligence and unusual features of face. (16) The Pelgere-Huët anomaly (PAH) is also characterized by similar manifestationsincluding short stature characteristics and damaged vision. PAH is the result ofthe atypical nucleus of the neutrophils. (17) Furthermore, PAH has been related with NBAS, (18) whose alterationstriggervery complicated morbidities like multisystemic phenotypes and ALF. (19)

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In reviewing all clinical features presented by this 5-year-old girl, the characteristics of NBAS-SOPH mutations are apparent and straightforward. In specific, this include: postnatal growth failure, small orbital cavities, narrow forehead, thin lips and facial asymmetry, hypoplastic cheekbones and a brachycephalic skull. (15) The evidence of the signs, symptoms, and parts of NBAS-SOPH mutations, as theoretically provided, were found on the girl. Therefore, the NBAS gene is linked with SOPH.

Clinical features in NBAS-SOPH	
Postnatal growth failure	Loose and senile skin with depressed turgor of tissue
Micromelia, brachydactyly	Bilateral optic nerve atrophy
Nonprogressive loss of visual acuity	Complete or incomplete achromatopsia
Hypolobulation of granulocyte nuclei	Brachycephalic skull with hypoplasia of the frontal and parie tubers
Narrow forehead	Long senile face with small features
Small orbits	Bilateral exophthalmos
Hypoplastic cheekbones	Straight nose with prominent glabella
Long philtrum	Thin lips
High voice with harsh timber	Short neck
Hypermobility of small joints	Muscular hypotonia
Wide feet with a high arch	Facial asymmetry
Thick and/or bushy eyebrows	Epicanthus
Sandal gap	Wide big toes

Fig: 6-Clinical features in NBAS-SOPH mutations (15)

➢ *The Fourth Research Journal.*

NBAS gene mutations have been recorded in skeletal dysplasia, isolated ALF and other complex phenotypes. The research article published in the PubMed directory seeks to identify NBAS's immunological consequences. (20) Primary immunodeficiencies (PIDs) are inherent heterogeneous conditions (21) that have been rare. However, through genetic dissection and finding new clinical phenotypes, (22) the number of PIDs, which arise from the mutation of genes for immune system development, (21) has emerged.

A population sample of three patients who had exhibited NBAS mutations detested by next-generation sequencing was considered for the experiment. Their ages were 5, 6, and 13. Blood samples were taken, immunological assays, chromosomal microarray, exome sequencing, and Sanger direct sequencing performed. (20) Besides, a literature review of PubMed indexed journals analyzing 74 patients with NBAS defects or SOPH syndrome was performed. (20)

Patient one used a wheelchair due to birth complications and bone fracture, he had an optic nerve atrophy at 18 months and age 3 and hypogammaglobulinemia. The patient also had pneumonia and recurrent bronchitis. At 11 years, the patient had short stature, progeroid facial appearance, brachycephalic skull, muscular hypotonia, thin lips, pointed chin, beaked nose and bilateral exophthalmos. He showed a considerable increase in liver enzymes, alanine aminotransferase, and delayed intellectual development. The second patient, a sister to patient one, had skeletal and craniofacial abnormalities from birth and low muscle tone. At six months, she suffered pharyngitis and gastroenteritis and hypogammaglobulinemia at four years. At the age of five, her dysmorphic features were similar to those of her brother, patient one. Samples from their parents exposed two innate variations in the NBAS gene. The third patient, not related to patients one and two, also shored related features to patients one and two. In total, 77 patients with the deficiency of NBAS were considered. (20) From the research, it is apparent that patients with deficient or altered NBAS gene exhibit similar or closely related symptoms, which are the SOPH symptoms. (23)

➢ *The Fifth Research Journal.*

The fifth and last research considered in this research paper is a case report of a female patient aged four years and nine months born at 38 weeks by healthy nonconsanguineous parents. The objective of the report is to highlight the changeability of clinical presentation related to NBAS deficiency. At five weeks, she was diagnosed with short stature, neutropenia, and low weight. Besides, she was later found with a high concentration of liver enzyme, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, cholinesterase, and glutamate dehydrogenase. (24) Further observations revealed reduction of subcutaneous fat, high and broad forehead, proptosis, smallmouth and thin lips, hypoplastic maxilla,convergent strabismusand large fontanels. She also had thick eyebrows, small feet and hands, and left hip dysplasia. (24)

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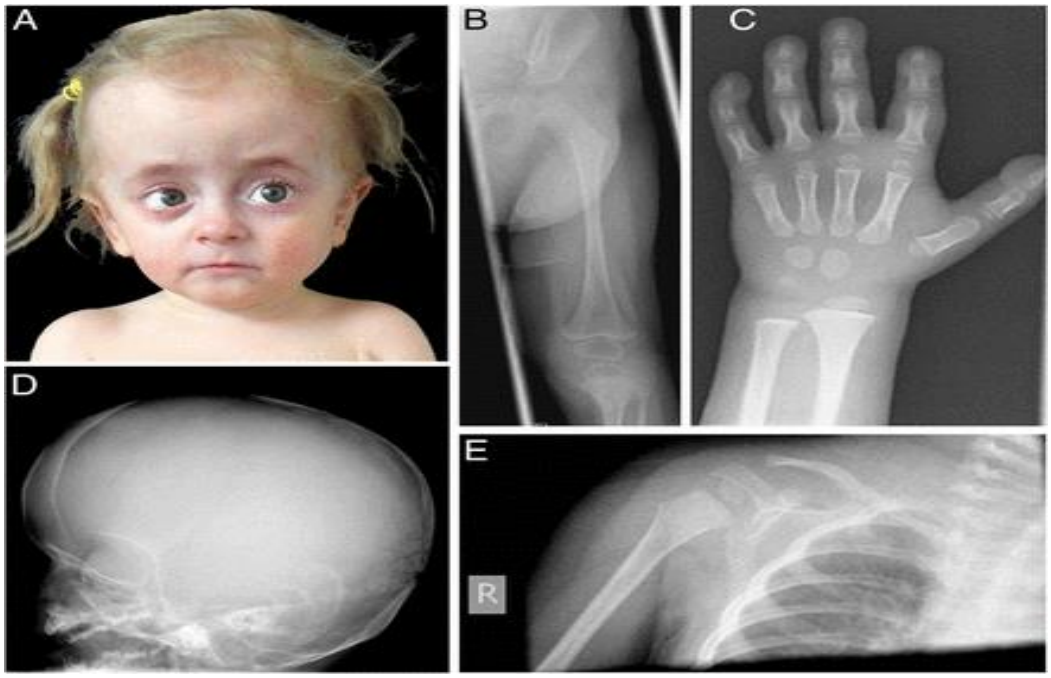

Fig: 7- Her radiographs. A-Facial dysmorphism at two years; B-delay in epiphyseal maturation and thin long tubular bones at 15 months; C-retarded maturation of phalanges, carpals, and metacarpals at three years and two months; D-Skull at 15 months, Hypoplastic maxilla, large fontanels, and poor ossification of calvarium; E-Epiphyseal delay of the right shoulder at 13 months. (24)

The patient revealed phenotypic resemblance with the 2 casesreported by Segarra et al., in which the mutation of the NBAS gene were apparent (25). Exhibited clinical features are similar to those of SOPH syndrome.

III. CONCLUSION AND RECOMMENDATIONS

SOPH syndrome leads to optic atrophy and achromatopasia, which, in turn, is triggered by cone dysfunction. All five experiments considered and narrated in the given paper demonstrate that SOPH syndrome is linked with deformities in the NBAS gene. Therefore, NBAS gene plays a crucial role in retinal homeostasis, making it indispensable to closely observe and investigate ocular abnormalities among SOPH patients. (26)

Syntaxin-18 SNARE complex is the main mediator of the retrograde intracellular vesicular movement. It was conjectured that NBAS gene was an essential constituent of this complex. (27) Apart of transporting, the NBAS gene manages gene expression when it is engaged in the mRNA decay surveillance path. (28) Accordingly, the NBAS gene is extensively phenotypic. SOPH develops from alterations in the NBAS gene (29), and a particular mutation that was analyzed in this paper is causing SOPH in the Yakut population of Siberia.

NBAS gene defects manifest in short stature, PHA, recurrent infections, optic nerve atrophy, anomaly in liver enzymes, skeletal dysplasia, proptosis, progeroid appearance, hypotonia and immunodeficiency. (30) Therefore, NBAS gene mutation is the triggering factorof SOPH syndrome.

Owing to the increase of NBAS gene mutation manifestations, ALF and SOPH syndrome, the next-generation sequencing should be enhanced and availed in all clinical setups to diagnose and revert detrimental consequences with the resultant disorders. Besides, some diseases being inherent, family history should be made mandatory for patients exhibiting NBAS- SOPH mutation characteristics.

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Journal title	Selection criteria	Objective/Study question	Data Size	Findings
Neuroblastoma amplified sequence gene is associated with a novel short stature syndrome characterized by optic nerve atrophy and Pelger-Huet anomaly. Journal of Medical Genetics. (1)	The journal has similar objectives and research question as to the study. The sample population composed of NBAS mutation patients, whom the study focuses also.	To determine the causative gene for SOPH	A total of 34 Patients. 22 females and 12 males.	NBAS is the causative gene for SOPH
Novel Neuroblastoma amplified sequence (NBAS) mutations in a Japanese boy with fever-triggered recurrent acute liver failure. (12)	The journal focuses on NBAS mutations just as the study.	To describe a patient with ALF and NBAS mutations	A total of 16 patients. 1 Japanese boy and a literature review of 15 other patients	Patients with ALF and NBAS mutations exhibit SOPH symptoms
Oculofacial alterations in NBAS-SOPH like mutations: A case report. European Journal of Ophthalmology. (15)	The paper reports the first NBAS mutation-based disease.	What are the immunological spectrum of a disease associated with NBAS deficiency?	1 Five-year-old girl.	NBAS gene is associated with SOPH.
Complex Multisystem Phenotype with Immunodeficiency Associated With NBAS Mutations: Reports of Three Patients and Review of the Literature. (20)	The sample population composed of bi-allelic NBAS mutation patients, whom the study focuses also.	What are the NBAS's immunological consequences?	A total of 77 patients. Samples from 3 patients and a literature review of 74 others.	Deficient or mutations in the NBAS gene exhibit similar or closely related symptoms to SOPH
Acute Liver Failure Meets SOPH Syndrome: A Case Report on an Intermediate Phenotype. (24)	The journal studies phenotypic expressions of NBAS deficiency and mutations, which the study also seeks to find.	To highlight the changeability of clinical presentation related to NBAS deficiency.	1 female patient	The clinical features she exhibited are similar to those of SOPH syndrome.

Table 2: Meta-data analysis of the findings of this essay.

FUTURE PERSPECTIVES

Gene mutations are connected to complex multisystem phenotypes with patients having immunodeficiency. (31) In the future, there will be improved technological methods of NBAS gene analysis and improved next-generation sequencing. As a result, more phenotypes of NBAS gene mutations are likely to be discovered.

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