Genetic Disorders Associated with Mutations in bHLH Transcription Factors: A Review

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirement for the degree of Bachelors in Biotechnology

Department of Mathematics and Natural Sciences

BRAC University

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Declaration

It is hereby declared that

- The thesis titled “Genetic Disorders Associated with Mutations in bHLH Transcription Factors: A Review” is my own original work completed by me as a prerequisite submission in requirement of the course “Biotech Project” coded as “BTE450” in the Biotechnology program of the Department of Mathematics and Natural Sciences of BRAC University, Dhaka.
- The thesis does not contain materials previously published or written a third party except where this is appropriately cited through full and accurately referencing.
- The thesis does not contain any material which has been accepted or submitted for any other degree.
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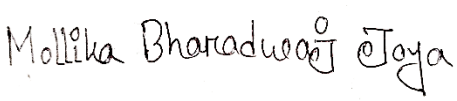

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Approval

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Abstract

bHLH proteins belong to a superfamily of proteins characterized by one of the largest dimerized transcriptional proteins. The main role of bHLH protein is in the developmental processes. They function as transcriptional factors, proteins that regulate the transcription of DNA into RNA. bHLH proteins are one of the most important proteins that help in many developmental processes during transcription process. Specifically, bHLH proteins play a role of determination of neural cells fates and ensure the exact number of specific neural cell production. The functions of bHLH proteins are strictly regulated. Mutations and deformations during transcription process on bHLH proteins can create genetic disorders. Disorders happen due to specific bHLH gene mutation and affects tissues. In this review, about 57 different genetic diseases are being discussed that are caused by mutations on different bHLH genes. Some of them are life threatening mutations and others make people handicapped for the rest of their life. Diseases like Cancer, Autoimmune disorders, Neurological disorders, Cardiovascular disorders, Obesity and many more can be caused by mis-regulations or mutations in regulatory sequences. The review sheds light on how bHLH protein mutations can cause widespread issues in different physiological systems.

Keywords

bHLH proteins, Transcriptional factors, Domain, Mutations, Chromosome, Inheritance.

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1. Introduction

Transcription is the process of copying components of DNA into RNA. Through this process DNA sequences or base pairs are being copied and then transcribed into RNA. The most important enzyme of transcriptional process is RNA Polymerase. When RNA Polymerase binds to the promoter sequences, the transcription process starts. RNA polymerase uses one of the DNA strands as a template to make a new, complementary RNA molecule. Transcription process is divided into 3 steps which are Initiation, Elongation and Termination. Termination depends on sequences in the RNA, which signal that the transcript is finished.

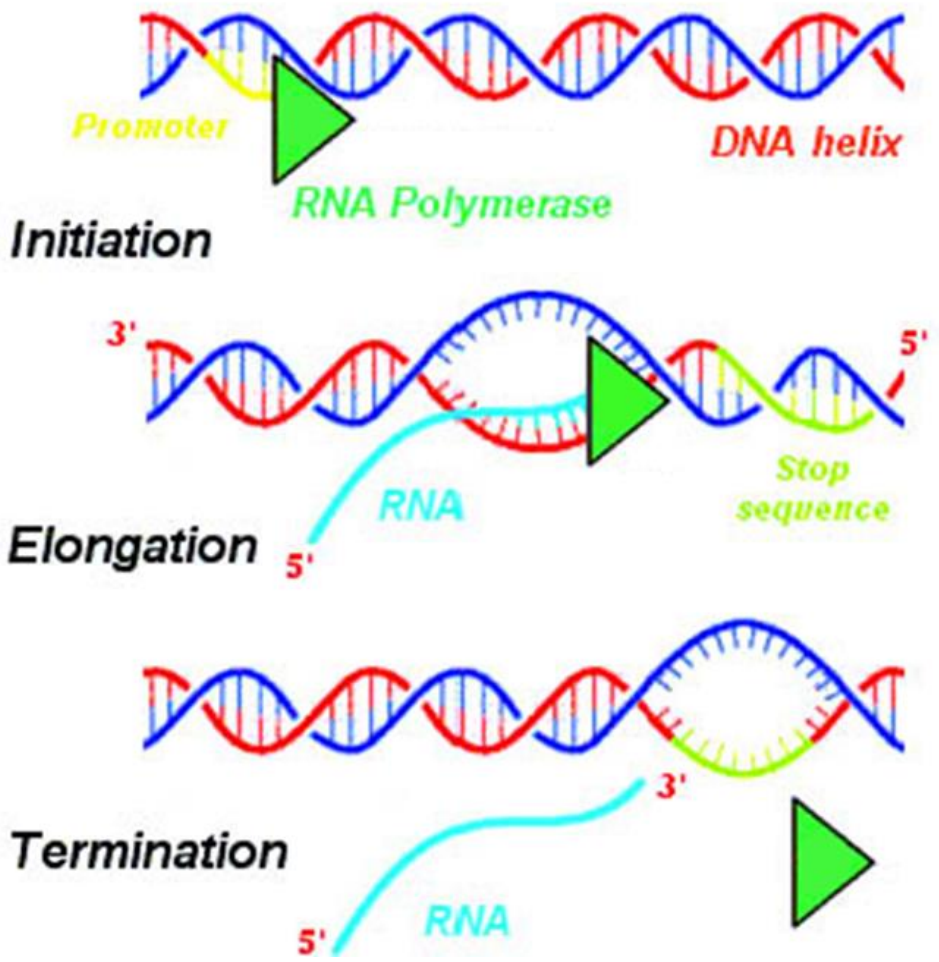

Fig: 1.1: Transcription Process

The gene expression programs that establish and maintain specific cell states in humans are controlled by thousands of transcription factors, cofactors and chromatin regulators. Mis-regulation of these gene expression programs can cause a broad range of diseases [1]. These mis-regulations are occurred because of mutations during transcription process. In this review paper almost 57 types of genetic bHLH mutated disorders have been discussed with their symptoms, affected tissues, mutated chromosomes, specific locations of mutation and some drugs against these disorders. Some oof these disorders are life threatening and other disorders make patients physically disable. The review paper discusses about bHLH proteins and its functions in details. Also shows details about the structures and classifications of bHLH proteins related disorders with figures.

1.1. bHLH protein

bHLH refers to Basic Helix-Loop-Helix Protein, which are transcriptional factors. bHLH proteins play important roles during the development of various metazoans like nematodes, vertebrates and flies [1]. bHLH protein malformation or mutation can create disease of human being, also other animals. Human diseases, specially Cancerogenesis diseases are involved with bHLH proteins [2]. bHLH domain is ~60 long [3]. Two alpha helices which is separated by a variable loop region follow bHLH which is composed by DNA binding basic region. HLH domain allows the formation of homodimeric and heterodimeric complexes of a family. [4]. These two basic domains are brought together through dimerization and bind specific hexanucleotide sequences. Not only in human but also many other organisms like animals, plants and fungi are where bHLH proteins have been found. bHLH protein was first identified in the murine transcriptional factors E12 and E47. This thing was first observed by scientist Murr and his colleagues [5]. bHLH works as important regulators of some purposes, like embryonic development, particularly in neurogenesis, myogenesis, heart development and hematopoiesis of eukaryotes [6]. bHLH have a great relationship or connection with Transcriptional regulators. bHLH proteins help transcriptional regulators to develop of sex determination factors and also in the development of the nervous system and the muscles [7]. bHLH protein is made of ~60 amino acids and each amino acid terminal ends are the basic domains where the

transcriptional factors bind. Consensus hexanucleotide sequence DNA is known as E-box. [8].

1.1.1. Classifications of bHLH proteins:

bHLH protein is classified based on tissue distributions. bHLH protein is divided into 4 major groups. Those groups are: A, B, C, D. In some cases, bHLH proteins are divided into 6 groups, then additionally group S and F are added [9].

Group A: This group is included tissue specific bHLH proteins. Also, the ubiquitously distributed Group A includes several tissue-specific bHLH proteins as well as the ubiquitously distributed E12/Daughterless type bHLH proteins are included. The tissue specific proteins from inactive homodimers and require the presence of a E12/Daughterless partner to form active heterodimers in many aspects. bHLH proteins that bind hexametric DNA sequences which is referred to "E-Boxes" (CANNTG) respectively CACCTG or CAGCTG (Group A) and CATGTTG (Group B) are include both Group A and Group B [10].

Group B: This group includes a large number of functionally unrelated proteins that is involved in many developmental purposes and also cellular purposes like Leucine Zipper (LZ). Group B proteins involves in protein Dimerization. Some proteins contain some special motifs. Like, The presence of proline rather than an arginine at a crucial position in the basic domain. These proteins bind preferentially based on the sequences that is referred to "N-boxes" which is (CACGCG or CACGAG), low affinity for "E-boxes. The HER protein is featured by the 4-amino acid WRPW domain. This domain allows the interaction with the Groucho repressor protein [11].

Group C: This group refers to the family of bHLH which is known as bHLH PAS protein. This PAS domain is ~260-310 amino acids long and also allow the dimerization between PAS protein the binding of small molecules and interaction with non-PAS proteins. This PAS protein has some features like neurogenesis, tracheal and salivary duct formation, toxin metabolism, circadian rhythms and response to hypoxia. bHLH PAS protein bind to ACGTG or GCGTG core sequences. [12].

Group D: These proteins are HLH proteins with a lack of basic domain and unable to bind DNA which is includes Id. Extramacrochaete protein referred to HLH proteins that lack a basic domain and are hence unable to bind.bHLH protein regulatory proteins are known to bind to a single DNA consensus sequence which is referred to “E-Box” [13].

These sequences of new genomes hve led to invent new bHLH families. This evolutionary classification extended the classification into 2 additional groups, which are Group E and Group F. But these 2 groups are still not enough explained or scientists did not give any vast information about these groups.

1.1.2. Structures of bHLH proteins:

bHLH superfamily structural data is still not well identified. The data of structures of bHLH proteins are relatively sparse. Only 9 bHLH protein structures have been clearly identified and explained in Protein Data Bank. The structure of CATH and SCOP proteins classifications classify 8 of these bHLH proteins into 1 superfamily [16]. Some of them have an additional zipper domain which is carboxy terminal to the HLH region and the two of the structures are heterodimer. Those two protein complexes are a Max-Myc complex and a Max-Mad complex. The rest complexes are homodimers. [14].

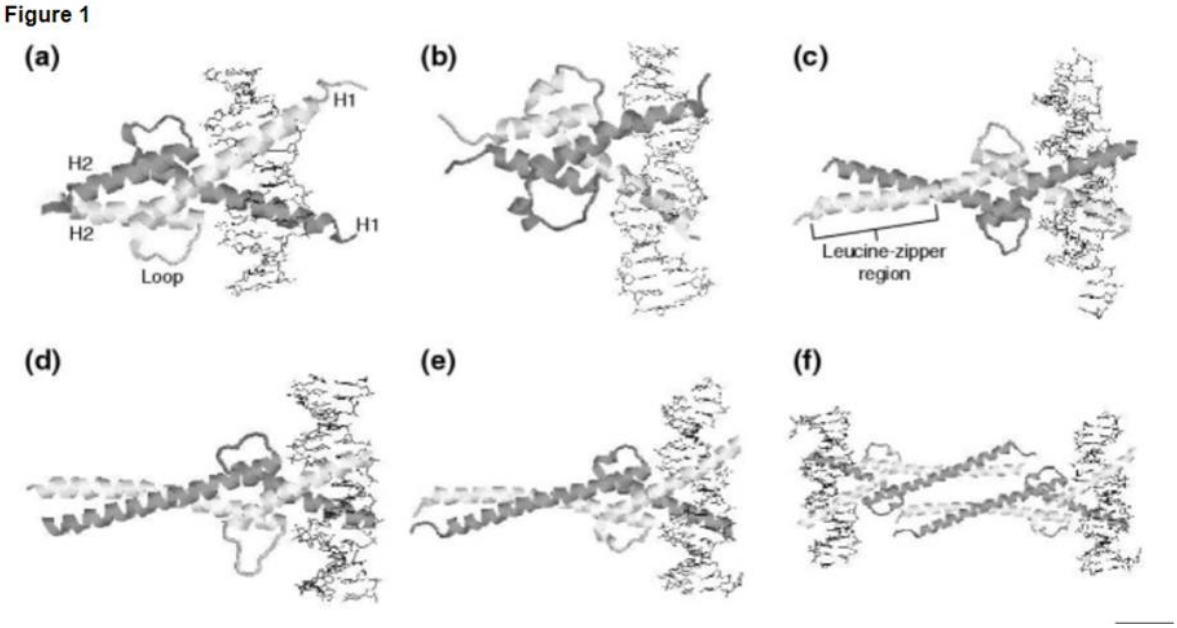

Fig 1.1: bHLH protein structures (Adapted from [4])

“In the diagram given upon, the protein is shown as a secondary structure and the DNA double helix is shown as stick representation. The figure (a) shows MyodD bHLH domain homodimer, figure (b) shows Pho4 bHLH domain homodimer, figure (c) shows SREBO-Ia bHLH domain homodimer, (d) Max-Mad heterodimer, figure (e) shows Max-Myc heterodimer, figure (f) shows Max-Myc heterodimer. In the figure (d-f) the Max monomer is shown in dark gray color. One of the functions of bHLH protein is creating diversity in sets of regulatory factors. For this, bHLH proteins form the heterogeneity of DNA sequences recognition and dimers [15].

1.1.3. Cell specific functions:

In case of cell specific functions of bHLH proteins, the proteins involve in cell fate determination in different cell linages. Then form an integral part of many processes, some are: neurogenesis, cardiogenesis, myogenesis and hematopoiesis [16]. bHLH functions are also present in neurogenesis in Drosophila. In vertebrates Mash 1, Math 1 and Neurogenesis are important in the initial determination of neurons. Here Nero D, Neuro D2, Math 2 and others are differentiation factors are some special functions of bHLH proteins. DHAND and eHAND are 2 important bHLH proteins in cardiac development in vertebrates. MyoD, MRF-4, Myf-5 and myogenin are myogenic regulatory factrs which regulate together both the establishment and differentiation of the myogenic lineage [18]. The stem cell leukemia protein which is a bHLH transcriptional factor, is important for hematopoiesis and is associated with acute T-cell leukemia [16].

1.1.4. Widely expressed functions:

Myc protin is one of the widely expressed bHLH protein. This is the gene which frequently affected gene in human tumor. Regulating translation initiation is one of the important functions of Myc protein and work as transcriptional activators when they form heterodimers with Max proteins [19]. Max proteins form both homodimers and heterodimers. Myc, Max and Mad all these genes have functions in cell cycle and have roles in transcription modules.

2. Functions of bHLH protein

bHLH protein is very essential in many developmental processes of our body, such as neurodevelopmental purpose, ventral telencephalon, dorsal telencephalon, spinal cord, hindbrain, retina etc.

2.1. bHLH gene functions in Ventral telencephalon:

In very early stage of Embryonic stage of Ventral Telencephalon the stage is divided into 3 parts. They are: Lateral (LGE), Medial (MGE) and Caudal (CGE) [20]. Huge number of projection neurons that remain in the Ventral Telencephalon is produced by these progenitors. These progenitors also have some purposes like populating the globus pallidus, amygdala and septum and striatum [21]. Ventrally produced neurons migrates to the dorsal domain of telencephalon. The neuronal differentiation of this part occurs fasters than dorsal domains. Ascl1 protein is essential for the generations of GABAergic neurons. Acsl1 is the only pro-neural bHLH gene expressed in the ventral telencephalon. Also, to specify an OPC fate in the embryonic stage of ventral telencephalon. Acsl1 promotes the proliferation of subpallial progenitors. This is a function that was uncovered through genome wide profiling target genes where most of them are involved in cell cycle regulations. Ascl1 missexpression can promote proliferation in case of mis=expressed in certain cellular contests are present [23].

2.2. bHLH gene function in the Spinal cord:

Dorsal progenitors in spinal cord are distributed in zone based dorsoventral axis. This zone range is from dp1 to dp6. Ventral zones ranges are from p0 to p3. This range is connected with motor neuron progenitor sone which is located between p2 and p3. Several bHLH genes are included in developing spinal cord. Some of them are Neurog1 (dp2, dp6, p0-p3), Neurog2 (dp2-dp6, p0-p2, pMN), Atoh (dp1), Olig2 (pMN), Olig3 (dp1-dp3, p0, p2, p3) and bHLHe22 (dp6, p1, p2) [24]. These genes are essential for differentiation of different spinal cord neurons. Ascl1 protein is also important for neurogenesis in spinal cord. Neurog2 binds to retinoic acid receptor then recruiting them to motor neuron differentiation genes. Then integrate RA motor neuron differentiation signal cord neurons and glia. Atoh1 is essential for specification of dorsal interneurons. It another function has

also cross repressive interactions with Neurog1 It is required for the differentiation of a distinct set of dorsal interneurons. The differentiation of VI interneurons is the function of bHLHE22.

2.3. bHLH gene in Hindbrain:

Dorsal hindbrain surrounds fourth ventricle. It is also known as Rhombic lip. Dorsal hindbrain is very essential. It gives rise to neurons that populate hindbrain nuclei [27]. Hindbrain locates on the caudal side of the isthmus. It is known as Mid-hindbrain boundary. Purkinje cells secret granule cell precursors in the outer EGL, express Atoh protein and proliferate in response to shh in the early postnatal or early embryonic stage [28]. One of the functions of Ascl1 is require for the differentiation of the subset of a subset of serotonergic neurons in hindbrains. In hindbrain it expressed in VZ progenitors. Another bHLH gene Neurog2+ progenitors give rise to Purkinje cells, which poorly develop in dendritic arbors [30].

2.4. bHLH gene in Retina:

Neurog2, Ascl1, Neurod4 and Atoh7 bHLH genes are expressed in embryonic retina. These genes differentiate Neurod1, Neurod2, Neurod6, bHLHbe22 and Olig2 [31]. Deformation of these genes creates developmental problems in retina in the embryonic period [32, 33]. Atoh7 the proneural gene is exceptional. It is important for the generation of most RGCs in mouse and Zebrafishes [34]. Neurog2 controls the RGC neurogenesis. Mutants in more bHLH genes are being found as a result of sever defect in retinal problems. Neurog2, Neurod4, Neurod1 retinas have only two cell layers which contains photoreceptors [37]. The absences or defects of these bHLH genes are upregulated as Ascl1 expression in Neurog2 mutants in the neocortex [38].

2.5. bHLH gene in Transcriptional Regulations:

Transcriptional, cofactors and chromatin regulators control the gene expression pf a specific cell. A simple deformation by any mutation can create life threatening disorders [39]. That is why transcriptional process need to be regulated properly to adjust the complexes and proteins [42, 43, 44]. Mediator is the key regulator of transcription process It interacts RNA polymerase II, coordinators and co-repressors [43, 44]. bHLH proteins

have another function that is to interact with the mediators and remodel histone acetyltransferases or deacyltransferases [45, 46]. SREBPs genes of human bind CBP/p300 acetyltransferase and MED15 subunits of the Mediator to active target genes [47]. For the specification of the blood lineage and maturation of several hematopoietic cells, Class II TFs TAL1 representative is required. TAL1 is the master of TF delineating of the cell fate and the identity of the progenitors and normal hematopoietic stem cells. It also regulates other hematopoietic transcriptional factors [48]. The HEY protein of bHLH-O family works as transcription repressors as well as transcription activators [49, 50]. It directly binds to DNA and interact to other histones deacetylases and others transcriptional factors. One of the essential roles of bHLH protein is to maintain the transcriptional regulation and the proper developments of different organs of a human body [51].

2.6. bHLH transcriptional factors as IDPs:

Intrinsically Discovered Proteins (IDPs) was discovered in 1990s. IDPs is a functional protein that have a well-defined structure, well ordered and a 3D structure [52]. The related disorders can be spread to the whole polypeptide chain or can be stayed limited to intrinsically disordered regions. Unusual compositions of amino acids give the sings of disorders [53, 54, 55, 56]. One of the most important roles of bHLH protein is controlling the developmental process of the organs. Some developments like Retinal development, Proliferation of progenitors, Neurogenesis and Gliogenesis etc. Complexes that bind to the specific promoters of the cause of the interaction between bHLH TFs and Homeodomain factors. The transcriptional of muscle specific gene depends on the interaction between bHLH proteins and TFs during the Skeletal muscle development [57, 58]. On the other hand, some bHLH proteins are involved in some disorder development processes. ID proteins are known for developing multiple cancers. Neurogenic bHLH transcription factor Neurogenin 2 (Ngn-2), had shown that IDR which phosphorylation regulates the activity of the protein [59, 60].

2.7. bHLH TFs effectors domains:

Some bHLH TFs of human can directly recruit RNA Polymerase. Some other bHLH TFs recruit accessary factors that specific phases of transcription processes [61]. Some TFs work as recruiter of cofactors. The coactivators and Corepressor are identified as mediators

of TFs in initially. The TF effector activity are frequently large multi subunit protein complexes that regulate transcription through several mechanisms [62]. Some examples of coactivators functions: p300 is sometimes used as marker enhancer which is associated with many TFs. Some TFs can recruit multiple cofactors. They have opposites effects of activators and repressor functions. MAX protein works as inhibitor when it binds to DNA as a heterodimer with MNT or MXDI. Also, woks as an activator when binds as a heterodimer with MYC protein [64, 65].

2.8. bHLH protein in sex determination:

bHLH proteins have a role in sex determination. Not only human sex determinations, bHLH proteins help to determine sex and the development of nervous system and muscle even in Yeast. bHLH proteins also regulate the root and help for the hair development [66, 67].

2.9. The Transcription Regulation and LLPS:

Scientists do not know much about the protein that is responsible of the formation of condensate, which is important for the transcriptional regulations [68]. They also do not know what bHLH protein exactly do as TFs in LLPS process. They are key workers in the development of important cell differentiation pathways. It is a Hypothesis that bHLH protein possess long IDs which interact with different partners and be engaged in LLPS. As this is and Hypothesis, some experimental proves are needed. An experiment shows that MyoD has the possibility to create LLPS and also says that bHLH TFs interact with the mediator subunits or other elements which modifies the chromatin accessibility [69].

3. Diseases associated with bHLH family gene mutations

In these tables, we can see the mutated bHLH genes with their associated proteins, and their references (Table 3.1). We also focus on the mutation causing those diseases, the inheritances of those specific disorders, and which chromosome we can find the mutation in (Table 3.2). Finally, we note the tissues that are affected by the mutations and the symptoms they cause (Table 3.3).

Table 3.1 Diseases caused from bHLH family gene mutations

Sl.	Disease name	Gene name	Protein	References
1.	Femur, Unilateral Bifid, with Monodactylous Ectrodactyly (GWC)	bHLHA9	-	https://omim.org/entry/228250
2.	Retinitis Pigmentosa 85 (RP85)	AHR	Aryl Hydrocarbon Receptor	https://omim.org/entry/618345
3.	Webb-Dattani Syndrome (WEDAS)	ARNT2	Aryl Hydrocarbon Receptor Nuclear Translocator 2	https://omim.org/entry/615926
4.	Persistent Hyperplastic Primary Vitreous, Autosomal Recessive (PHPVAR)	ATOH7	Protein Atonal homolog 7	https://omim.org/entry/221900
5.	Syndactyly, Mesoaxial Synostotic, with Phalangeal Reduction (MSSD)	bHLHA9	Class A Basic-Helix-Loop-Helix protein 9	https://omim.org/entry/609432
6.	Camptosynpolydactyly, Complex (CCSPD)	bHLHA9	Class A Basic-Helix-Loop-Helix protein 9	https://omim.org/entry/607539

Sl.	Disease name	Gene name	Protein	References
7.	Erythrocytosis, Familial, 4 (ECYT4)	EPAS1	Endothelial PAS domain containing protein 1	https://omim.org/entry/611783
8.	Premature Ovarian Failure 6 (POF6)	FIGLA	Factor in the gram line alpha	https://omim.org/entry/612310
9.	Spondylocostal Dysostosis 4, Autosomal Recessive (SCDO4)	HES7	Transcription factor HES7	https://omim.org/entry/613686
10.	Leukemia	MIR27A (MicroRNA 27a)	Protein LYL-1	-
11.	Pheochromocytoma (PCC)	MAX	Protein MAX	https://omim.org/entry/171300
12.	Spondylocostal Dysostosis 2, (Autosomal Recessive (SCDO2)	MESP2	Mesoderm posterior protein	https://omim.org/entry/103500
13.	Waardenburg Syndrome, Type 2 (WS2A)	MIFT	Microphthalmia associated transcription factor	https://omim.org/entry/193510
14.	Waardenburg Syndrome, Type 2a (WS2A)	MIFT	Microphthalmia associated transcription factor	https://omim.org/entry/193510
15.	Coloboma Osteopetrosis, Microphthalmia, Microphthalmia, Albinism and Deafness (COMMAD)	MIFT	Microphthalmia associated transcription factor	https://omim.org/entry/617306

Sl.	Disease name	Gene name	Protein	References
16.	Melanoma, Cutaneous Malignant 8 (CMM8)	MIFT	Microphthalmia Associated Transcription Factor	https://omim.org/entry/614456
17.	Prostate Cancer (PC)	CHEK2	Max-interacting protein 1	https://omim.org/entry/176807
18.	Myopathy, Congenital with Diaphragmatic Defects, Respiratory Insufficiency and Dysmorphic Facies (MYODRIF)	MYOD1	Myoblast determination Protein 1	https://omim.org/entry/618975
19.	Chondrosarcoma (CHDSA)	EXT1	Nuclear receptor coactivator 2	https://omim.org/entry/215300
20.	Maturity Onset Diabetes of the Young, Type 6 (MODY6)	NEUROD1	Neurogenic Differentiation Factor 1	https://omim.org/entry/606394
21.	Type 2 Diabetes Mellitus (T2D)	NEUROD1	Neurogenic Differentiation Factor 1	https://omim.org/entry/125853
22.	Developmental and Epileptic Encephalopathy 72 (DEE72)	NEUROD2 (Neuronal Differentiation 2)	Neurogenic differentiation factor 1	https://omim.org/entry/618374
23.	Diarrhea 4, Malabsorptive, Congenital (DIAR4)	NEUROG3 (Neurogenin 3)	Neurogenin 3	https://omim.org/entry/610370
24.	Pancreatic and Cerebellar Agenesis (PACA)	PTF1A	Pancreas Transcription Factor 1 Subunit Alpha	https://omim.org/entry/609069
25.	Pancreatic Agenesis 2 (PAGEN2)	PTF1A	Pancreas Transcription Factor 1 Subunit Alpha	https://omim.org/entry/615935

Sl.	Disease name	Gene name	Protein	References
26.	Spermatogenic Failure 32 (SPGF32)	SOHLH1	Spermatogenesis and Oogenesis Specific Basic-Helix-Loop-Helix containing protein 1	https://omim.org/entry/618115
27.	Ovarian Dysgenesis 5 (ODG5)	SOHLH1	Spermatogenesis and Oogenesis Specific Basic-Helix-Loop-Helix containing protein 1	https://omim.org/entry/617690
28.	Erythroleukemia	EPOR (Erythropoietin Receptor)	T-cell lymphocytic leukemia protein 1	-
29.	T-Cell Acute Lymphoblastic Leukemia	ABL1	T-cell lymphocytic leukemia protein 2	-
30.	Craniosynostosis (CSO)	FGFR2	Transcription factor 12	-
31.	Agammaglobulinemia 8a, Autosomal Dominant (AGM8A)	TCF3	Transcription Factor E2 Alpha	https://omim.org/entry/616941
32.	Saethre-Chotzen Syndrome (SCS)	TWIST1	Twist related protein 1	https://omim.org/entry/101400
33.	Robinow-Sorauf Syndrome (RSS)	TWIST1	Twist related protein 1	https://omim.org/entry/180750
34.	Craniosynostosis 1 (CRS1)	TWIST1	Twist related protein 1	https://omim.org/entry/123100
35.	Sweeney-Cox Syndrome (SWCOS)	TWIST1	Twist related protein 1	https://omim.org/entry/617746
36.	Focal Facial Dermal Dysplasia 3, Setleis Typer (FFDD3)	TWIST2	Twist related protein 2	https://omim.org/entry/227260

Sl.	Disease name	Gene name	Protein	References
37.	Barber-Say Syndrome (BBRSAY)	TWIST2	Twist related protein 2	https://omim.org/entry/209885
38.	Ablepharon-Macrostomia Syndrome (AMS)	TWIST2	Twist related protein 2	https://omim.org/entry/200110
39.	Hyperlipidemia, Familial Combined, 3 (FCHL3)	LPL	Upstream stimulatory factor 1	https://omim.org/entry/144250
40.	Delayed Sleep Phase Disorder (DSPD)	CRY1 (Cryptochrome Circadian Regulator 1)	Cryptochrome-1	https://omim.org/entry/614163
41.	Central Hypoventilation Syndrome, Congenital, 1 (CCHS1)	PHOX2B	Paired mesoderm Homeobox protein 2B	https://omim.org/entry/209880
42.	Hermansky-Pudlak Syndrome 2 (HPS2)	AP3B1	AP-3 Complex Subunit Beta 1	https://omim.org/entry/608233
43.	Fructosuria, Essential (FRUCT)	KHK (Ketohexokinase)	Ketohexokinase	https://omim.org/entry/229800
44.	Fanconi Anemia, Complementation Group T (FANCT)	UBE2T	Ubiquitin Conjugating enzyme	https://omim.org/entry/616435
45.	Short Sleep, Familial Natural, 1 (FNSS1)	bHLHE41	Class E Basic-Helix-Loop-Helix protein 41	https://omim.org/entry/612975
46.	Delayed Sleep Phase Disorder (DSPD)	CRY1 (Cryptochrome Circadian Regulator 1)	Cryptochrome-1	https://omim.org/entry/614163

Sl.	Disease name	Gene name	Protein	References
47.	Hypoplastic Left Heart Syndrome (HLHS)	TBX20	-	-
48.	Cardiomyopathy, Dilated, 1a (CMD1A)	LMNA (Lamin A/C)	Prelamin-A/C	https://omim.org/entry/115200
49.	Bietti Crystalline Corneoretinal Dystrophy (BCD)	CYP4V2	Cytochrome P4504V2	https://omim.org/entry/210370
50.	Chromosome 1p36 Deletion Syndrome	SPEN (Spen Family Transcriptional Repressor)	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1	-
51.	Fibrodysplasia Ossificans Progressiva (FOP)	ACVR1	Activin Reception Type 1	https://omim.org/entry/135100
52.	Myasthenic Syndrome, Congenital, 12 (CMS12)	GFPT1	Glutamine Fructose 6 phosphate aminotransferase 1	https://omim.org/entry/610542
53.	D2-Hydroxyglutaric Aciduria 2 (D2HGA2)	IDH2	-	https://omim.org/entry/613657
54.	Spastic Paraplegia 24, Autosomal Recessive (SPG24)	SPG24	Dual serine / threonine and tyrosine protein kinase	https://omim.org/entry/607584
55.	Mucoepithelial Dysplasia, Hereditary (HMD)	SREBF1	Sterol Regulatory Element Binding protein 1	https://omim.org/entry/158310
56.	Elsahy-Waters Syndrome (ESWS)	CDH11	Cadherin-11	https://omim.org/entry/211380
57.	Renal Dysplasia	GATA3	Serine / threonine protein kinase Nek1	-

Sl.	Disease name	Gene name	Protein	References
58.	Cowden Syndrome 1 (CWS1)	PTEN	Phosphatidylinositol 3, 4, 5-Triphosphate 3-phosphate and dual specificity protein phosphatase	https://omim.org/entry/158350

Table 3.2 Disease Inheritance and Genomic Context

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
1.	Femur, Unilateral Bifid, with Monodactylous Ectrodactyly (GWC)	Autosomal Dominant	-	-
2.	Retinitis Pigmentosa 85 (RP85)	Autosomal Recessive	Homozygous mutation	Chromosome 7p21.
3.	Webb-Dattani Syndrome (WEDAS)	Autosomal Recessive	Homozygous mutation	chromosome 15q25.
4.	Persistent Hyperplastic Primary Vitreous, Autosomal Recessive (PHPVAR)	Autosomal Recessive	Homozygous mutation	chromosome 10q21
5.	Syndactyly, Mesoaxial Synostotic, with Phalangeal Reduction (MSSD)	Autosomal Recessive	Homozygous mutation	chromosome 17p13
6.	Camptosynpolydactyly, Complex (CCSPD)	Autosomal Recessive	Homozygous mutation	chromosome 17p13
7.	Erythrocytosis, Familial, 4 (ECYT4)	Autosomal Dominant	Gain of function mutation	chromosome 2p21

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
8.	Premature Ovarian Failure 6 (POF6)	Autosomal Dominant	Heterozygous or Homozygous mutation	chromosome 2p13
9.	Spondylocostal Dysostosis 4, Autosomal Recessive (SCDO4)	Autosomal Recessive	Homozygous or compound Heterozygous mutation	chromosome 17p13
10.	Leukemia	-	-	-
11.	Pheochromocytoma (PCC)	-	Germline mutation	chromosome 2q11 and chromosome 14q23
12.	Spondylocostal Dysostosis 2, (Autosomal Recessive (SCDO2)	Autosomal dominant	Heterozygous mutation	chromosome 3p13
13.	Waardenburg Syndrome, Type 2 (WS2A)	Autosomal Dominant	Heterozygous mutation	chromosome 3p13
14.	Waardenburg Syndrome, Type 2a (WS2A)	Autosomal Dominant	Heterozygous mutation	chromosome 3p13
15.	Coloboma Osteopetrosis, Microphthalmia, Microphthalmia, Albinism and Deafness (COMMAD)	Autosomal recessive	Compound Heterozygous mutation	chromosome 3p13
16.	Melanoma, Cutaneous Malignant 8 (CMM8)	-	Heterozygous mutation	chromosome 3p13
17.	Prostate Cancer (PC)	Somatic mutation	Trait Locus	chromosome 19q
18.	Myopathy, Congenital with Diaphragmatic Defects,	Autosomal Recessive	Homozygous mutation	chromosome 11p15

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
	Respiratory Insufficiency and Dysmorphic Facies (MYODRIF)			
19.	Chondrosarcoma (CHDSA)	Somatic Mutation	Constitutional or Somatic mutation	chromosome 8q24
20.	Maturity Onset Diabetes of the Young, Type 6 (MODY6)	-	Heterozygous mutation	chromosome 2q31
21.	Type 2 Diabetes Mellitus (T2D)	-	More than 1 gene mutation	-
22.	Developmental and Epileptic Encephalopathy 72 (DEE72)	Autosomal Dominant	heterozygous mutation	chromosome 17q12
23.	Diarrhea 4, Malabsorptive, Congenital (DIAR4)	Autosomal Recessive	mutation in the gene encoding neurogenin-3	chromosome 10q22
24.	Pancreatic and Cerebellar Agenesis (PACA)	Autosomal Recessive	Homozygous mutation	chromosome 10p12
25.	Pancreatic Agenesis 2 (PAGEN2)	Autosomal Recessive	Homozygous or Compound Heterozygous mutation	chromosome 10p12
26.	Spermatogenic Failure 32 (SPGF32)	Autosomal Dominant	Heterozygous mutation	chromosome 9q34
27.	Ovarian Dysgenesis 5 (ODG5)	Autosomal Recessive	Homozygous mutation	chromosome 9q34
28.	Erythroleukemia	-	-	-

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
29.	T-Cell Acute Lymphoblastic Leukemia	-	-	-
30.	Craniosynostosis (CSO)	Autosomal Dominant, Autosomal Recessive, X-linked Recessive	-	-
31.	Agammaglobulinemia 8a, Autosomal Dominant (AGM8A)	Autosomal Dominant	Heterozygous, Dominant, Negative mutation	chromosome 19p13
32.	Saethre-Chotzen Syndrome (SCS)	Autosomal Dominant	Heterozygous mutation	chromosome 7p21
33.	Robinow-Sorauf Syndrome (RSS)	Autosomal Dominant	Heterozygous mutation	chromosome 7p21
34.	Craniosynostosis 1 (CRS1)	-	Heterozygous mutation	chromosome 7p21
35.	Sweeney-Cox Syndrome (SWCOS)	Autosomal Dominant	Heterozygous mutation	chromosome 7p21
36.	Focal Facial Dermal Dysplasia 3, Setleis Typer (FFDD3)	Autosomal Recessive	Homozygous mutation	chromosome 2q37
37.	Barber-Say Syndrome (BBRSAY)	Autosomal dominant, Autosomal recessive	Heterozygous mutation	chromosome 2q37
38.	Ablepharon-Macrostomia Syndrome (AMS)	Autosomal Dominant	Heterozygous mutation	chromosome 2q37

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
39.	Hyperlipidemia, Familial Combined, 3 (FCHL3)	Autosomal Dominant	Heterozygous mutation	chromosome 8p21
40.	Delayed Sleep Phase Disorder (DSPD)	Autosomal Dominant	Heterozygous mutation	chromosome 12q23
41.	Central Hypoventilation Syndrome, Congenital, 1 (CCHS1)	Autosomal Dominant	Heterozygous mutation	chromosome 4p13
42.	Hermansky-Pudlak Syndrome 2 (HPS2)	Autosomal Dominant	Heterozygous mutation	chromosome 5q14
43.	Fructosuria, Essential (FRUCT)	Autosomal Recessive	heterozygous mutation in the KHK gene	chromosome 2p23
44.	Fanconi Anemia, Complementation Group T (FANCT)	Autosomal Recessive	Heterozygous mutation	chromosome 1q32
45.	Short Sleep, Familial Natural, 1 (FNSS1)	Autosomal Dominant	Heterozygous mutation	chromosome 12p12
46.	Delayed Sleep Phase Disorder (DSPD)	Autosomal Dominant	heterozygous mutation in the CRY1 gene	chromosome 12q23
47.	Hypoplastic Left Heart Syndrome (HLHS)	-	Multifactorial combination of Genetic mutation	-
48.	Cardiomyopathy, Dilated, 1a (CMD1A)	Autosomal Dominant	heterozygous mutation in	chromosome 1q22

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
			the lamin A/C gene	
49.	Bietti Crystalline Corneoretinal Dystrophy (BCD)	Autosomal Recessive	Homozygous or Compound Heterozygous mutation	chromosome 4q35
50.	Chromosome 1p36 Deletion Syndrome	Multigenic/ multifactorial	-	-
51.	Fibrodysplasia Ossificans Progressiva (FOP)	Autosomal Dominant	Heterozygous mutation	chromosome 2q24
52.	Myasthenic Syndrome, Congenital, 12 (CMS12)	Autosomal Recessive	Homozygous or Compound Heterozygous mutation	chromosome 2p13
53.	D2-Hydroxyglutaric Aciduria 2 (D2HGA2)	-	Heterozygous mutation	chromosome 15q26
54.	Spastic Paraplegia 24, Autosomal Recessive (SPG24)	Autosomal Recessive	-	chromosome 13q14
55.	Mucoepithelial Dysplasia, Hereditary (HMD)	Autosomal Dominant	Heterozygous mutation	chromosome 17p11
56.	Elsahy-Waters Syndrome (ESWS)	Autosomal Recessive	Homozygous mutation	chromosome 16q21
57.	Renal Dysplasia	Autosomal Dominant	Homozygous / Heterozygous mutation	-

SL	Disease name	Inheritance	Mutation information	Affected Chromosomes
58.	Cowden Syndrome 1 (CWS1)	Autosomal Dominant	Heterozygous Germline mutation	chromosome 10q23

Table 3.3 Affected Tissue and Symptoms of the Diseases

SL	Disease name	Tissue affected	Symptoms
1.	Femur, Unilateral Bifid, with Monodactylous Ectrodactyly (GWC)	bone and heart	Skeletal system
2.	Retinitis Pigmentosa 85 (RP85)	retina	Sensory system
3.	Webb-Dattani Syndrome (WEDAS)	pituitary, temporal lobe and brain	Muscularly system, Nervous system
4.	Persistent Hyperplastic Primary Vitreous, Autosomal Recessive (PHPVAR)	eye, retina and prostate	Sensory system
5.	Syndactyly, Mesoaxial Synostotic, with Phalangeal Reduction (MSSD)	bone, heart and skin	Skeletal system, Cardiac system, Skin and Epithelial system
6.	Camptosynpolydactyly, Complex (CCSPD)	hands	Skeletal system
7.	Erythrocytosis, Familial, 4 (ECYT4)	blood	Circulatory system
8.	Premature Ovarian Failure 6 (POF6)	uterus and ovary	Reproductive system
9.	Spondylocostal Dysostosis 4, Autosomal Recessive (SCDO4)	bone	Skeletal system
10.	Leukemia	myeloid, bone marrow and t cells	Circulatory system
11.	Pheochromocytoma (PCC)	adrenal gland, heart and thyroid	Cardiac system, Endocrine system

SL	Disease name	Tissue affected	Symptoms
12.	Spondylocostal Dysostosis 2, (Autosomal Recessive (SCDO2)	skin, eye and retina	Sensory system, Skin and Epithelial system
13.	Waardenburg Syndrome, Type 2 (WS2A)	eye and skin	Sensory system, Skin and Epithelial system
14.	Waardenburg Syndrome, Type 2a (WS2A)	eye and skin	Sensory system, Skin and Epithelial system
15.	Coloboma Osteopetrosis, Microphthalmia, Microphthalmia, Albinism and Deafness (COMMAD)	skin, bone and eye	Sensory system, Skin and Epithelial system and Skeletal system
16.	Melanoma, Cutaneous Malignant 8 (CMM8)	skin, brain and t cells	Nervous system, Sensory system and Circulatory system
17.	Prostate Cancer (PC)	prostate, bone and lymph node	Skeletal system, Reproductive system and Circulatory system
18.	Myopathy, Congenital with Diaphragmatic Defects, Respiratory Insufficiency and Dysmorphic Facies (MYODRIF)	lung, kidney and heart	Cardiac system, Respiratory system and Renal system
19.	Chondrosarcoma (CHDSA)	bone, brain and breast	Skin system, Skeletal system and Nervous system
20.	Maturity Onset Diabetes of the Young, Type 6 (MODY6)	Nervous system development and Glucose / Energy Metabolism	Nervous system, Gastrointestinal system
21.	Type 2 Diabetes Mellitus (T2D)	Pancreas and Adipose	Gastrointestinal system and Others

SL	Disease name	Tissue affected	Symptoms
22.	Developmental and Epileptic Encephalopathy 72 (DEE72)	eye	Sensory system
23.	Diarrhea 4, Malabsorptive, Congenital (DIAR4)	liver	Gastrointestinal system
24.	Pancreatic and Cerebellar Agenesis (PACA)	pancreas, dorsal root ganglion and endothelial	Endocrine system and Gastrointestinal system
25.	Pancreatic Agenesis 2 (PAGEN2)	pancreas and liver	Gastrointestinal system and Endocrine system
26.	Spermatogenic Failure 32 (SPGF32)	testes	Reproductive system
27.	Ovarian Dysgenesis 5 (ODG5)	uterus and bone	Reproductive system and Skeletal system
28.	Erythroleukemia	myeloid, bone marrow and bone	Circulatory system
29.	T-Cell Acute Lymphoblastic Leukemia	bone marrow, t cells and bone	Circulatory system and Skeletal system
30.	Craniosynostosis (CSO)	bone	Skeletal system
31.	Agammaglobulinemia 8a, Autosomal Dominant (AGM8A)	B cells	Circulatory system
32.	Saethre-Chotzen Syndrome (SCS)	skull, bone and eye	Skeletal system and Circulatory system
33.	Robinow-Sorauf Syndrome (RSS)	Face, nose, toe	Sensory system, Skin and Epithelial system
34.	Craniosynostosis 1 (CRS1)	eye, brain and spleen	Gastrointestinal system and Sensory system
35.	Sweeney-Cox Syndrome (SWCOS)	spleen, cerebellum and bone	Gastrointestinal system and Skeletal system
36.	Focal Facial Dermal Dysplasia 3, Setleis Typer (FFDD3)	Skin and eye	Sensory system, Skin and Epithelial system

SL	Disease name	Tissue affected	Symptoms
37.	Barber-Say Syndrome (BBRSAY)	skin, eye and breast	Skin and Epithelial system, Sensory system
38.	Ablepharon-Macrostomia Syndrome (AMS)	eye, skin and breast	Skin and Epithelial system and Sensory system
39.	Hyperlipidemia, Familial Combined, 3 (FCHL3)	heart, liver and endothelial	Gastrointestinal systems, Cardiac system, Skin and Epithelial system
40.	Delayed Sleep Phase Disorder (DSPD)	brain, spinal cord and fetal brain	Nervous system and Skeletal system
41.	Central Hypoventilation Syndrome, Congenital, 1 (CCHS1)	lung, heart and brain	Circulatory system, Cardiac system, Nervous system
42.	Hermansky-Pudlak Syndrome 2 (HPS2)	skin, b lymphoblasts and lung	Skin and Epithelial system, Respiratory system
43.	Fructosuria, Essential (FRUCT)	Liver	Gastrointestinal system
44.	Fanconi Anemia, Complementation Group T (FANCT)	bone marrow and bone	Circulatory system, Skeletal system
45.	Short Sleep, Familial Natural, 1 (FNSS1)	-	Others
46.	Delayed Sleep Phase Disorder (DSPD)	brain, spinal cord and fetal brain	Nervous system, Skeletal system
47.	Hypoplastic Left Heart Syndrome (HLHS)	heart, skin and brain	Cardiac system, Skin and Epithelial system, Nervous system

SL	Disease name	Tissue affected	Symptoms
48.	Cardiomyopathy, Dilated, 1a (CMD1A)	heart, liver and skeletal muscle	Muscular system, Cardiac system, Skeletal system
49.	Bietti Crystalline Corneoretinal Dystrophy (BCD)	retina, eye and skin	Nervous system, Skin and Epithelial system
50.	Chromosome 1p36 Deletion Syndrome	heart, kidney and eye	Sensory system, Cardiac system, Renal system
51.	Fibrodysplasia Ossificans Progressiva (FOP)	bone, skeletal muscle and skin	Skeletal system, Skin and Epithelial system
52.	Myasthenic Syndrome, Congenital, 12 (CMS12)	-	Muscular system
53.	D2-Hydroxyglutaric Aciduria 2 (D2HGA2)	Brain, bone and eye	Nervous system, Skeletal system
54.	Spastic Paraplegia 24, Autosomal Recessive (SPG24)	-	Gastrointestinal system, Muscular system
55.	Mucoepithelial Dysplasia, Hereditary (HMD)	skin, eye and tongue	Skin and Epithelial system, Nervous system
56.	Elsahy-Waters Syndrome (ESWS)	skin, brain and spinal cord	Skin and Epithelial system, Nervous system, Skeletal system
57.	Renal Dysplasia	kidney, testis and uterus	Renal system, Reproductive system
58.	Cowden Syndrome 1 (CWS1)	cerebellum, skin and thyroid	Skin and Epithelial system, Circulatory system.

4. Statistical Analysis of the Diseases

Diseases that are caused by transcriptional factors mutations affect some specific tissues and shows different symptoms that are sometimes severe, sometime mild. As these disorders are genetic disorders, they show different inheritances. Scientists were able to find the specific mutated genes and chromosomes and their locations. Some drugs are also invented by scientists but most of them are not curable. Patients genetically get these disorders from their parents but some occur later in their lives. Some statistics of those responsible tissues, genes, chromosomes, showing symptoms, inheritances are shown below by using Pie charts and Bar charts. These charts show the percentages of these categories.

- **Affected Tissues:**

Fig 4.1 observes the tissues affected by these diseases. The bar chart shows the results of the percentages of the affected tissue by the mutations. The chart statistics shows that the highest affected tissues are belong from Nervous system organs. On the other hand, the rate of Hormonal glands tissues being affected is the lowest. But the rate of Adipose tissues being mutated is much lower than the Hormonal glands. The second highest organ tissues that get affected by the mutation is Musculoskeletal organs. Next highest organs are Circulatory system organs and Skin and External organs tissues. Sensory organ tissues are the 5th highest affected tissues, Internal organ tissues are the 6th highest, Reproductive organ tissues are the 7th highest, Hormonal glands are the 8th highest and the others tissues like Adipose tissues are the lowest affected tissues that are being mutated. The nervous system related tissues are affected by the mutation most. About 24 disorders of bHLH gene mutation affects the nervous system related tissues. 2nd highest affected tissues are under Musculoskeletal system related tissues, it occupies about 19 disorders. Skin and External system and Circulatory system related tissues occupies about 18 disorders. Sensory organ tissues occupy 16 disorders. Internal organ tissues occupy 13 disorders. Reproductive system related tissues are mutated by 6 disorders. Hormonal glands related tissues are mutated by 4 disorders. Lastly, others tissues that are not related with these organ systems are mutated by about 2 disorders.

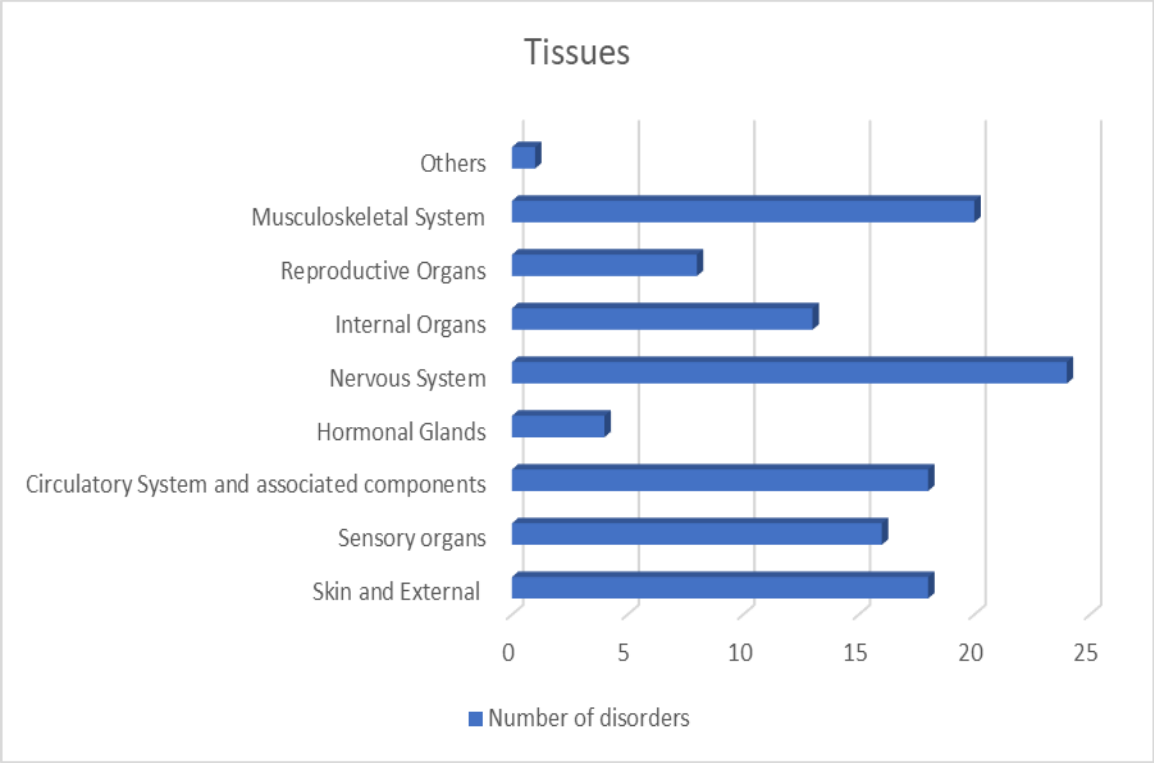

Fig 4.1: Affected Tissues in bHLH mutations.

- **Inheritance:**

Fig 4.2 focuses the percentages of inheritances of the mutated genes. Autosomal Dominant shows the highest result with achieving 43% of the chart. Next is Autosomal Recessive disorders which is 34%. Next percentage is for that section which is still unidentified, it achieves 16%. Next is Somatic mutation, which is only 3%. Then Multi-mutations or multifunctional, which is 2% and lastly, the X-linked mutation is only 2%. Autosomal Dominant is a type of inheritance that is a genetic condition that can pass to children from their parents. The children have 50% of chance of getting affected by the mutated gene if their parents have the mutated gene in their body. Both male and female children are equally having the chances of got affected from their parents. Autosomal Recessive condition is also a type of inheritance where children got affected by any disorder caused by mutated gene from their parents. But in that case parents play a role of carrier. Usually parents do not show any sign or symptoms of the specific disorder, the pass the gene to their children and in children body it become active and the children got affected.

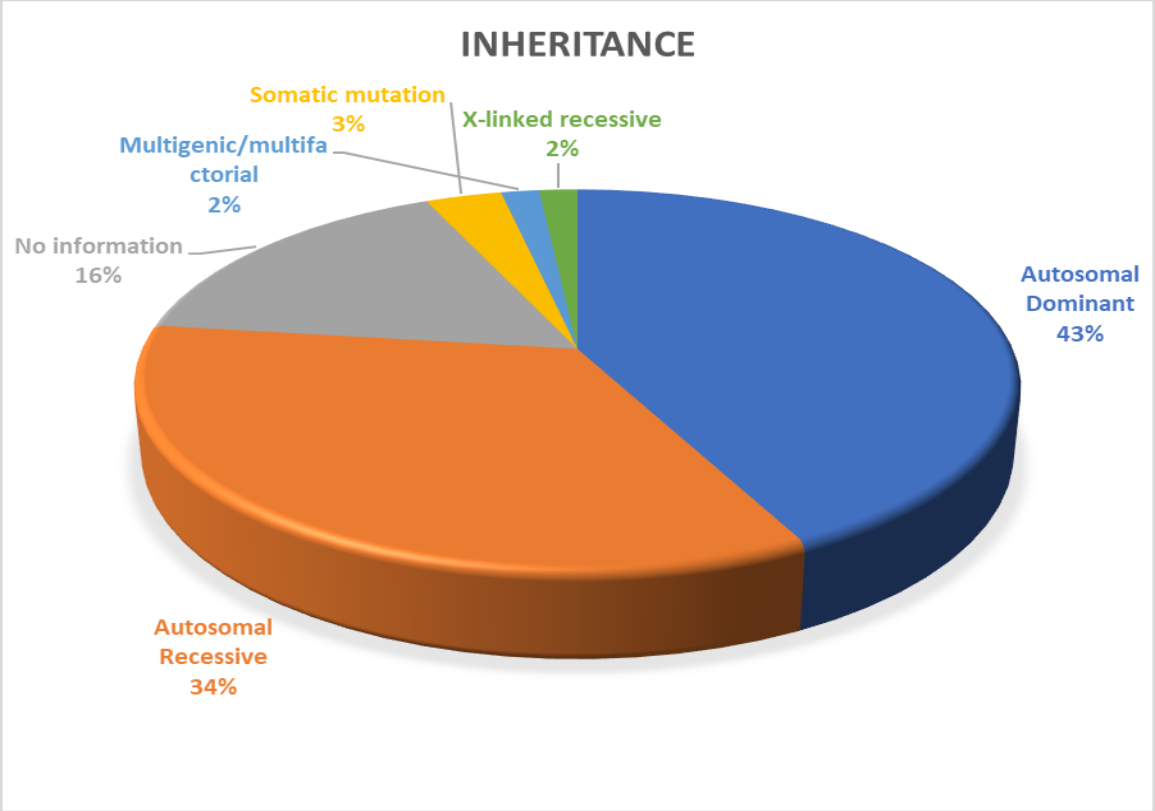

Fig 4.2: Inheritance patterns of bHLH-associated diseases.

- **Mutations:**

Fig 4.3 illustrated the different types of mutations found in bHLH genes. The highest range of the chart achieves the Heterozygous mutations by 47%. 2nd highest is Homozygous mutations. 3rd highest is Somatic mutations with 2% and the lowest are Germline mutations and Germline mutations by 1% of the chart. Mutation is an incident of the alteration of nucleic sequences of an organism. Homozygous means the inheritance of genes of a child from his/her biological parents. Heterozygous means the inherit of two different genes of a child from his/her biological parents. Germline mutation is a type of mutation in germline where a gene change occurs in reproductive cell and remains active to the DNA and the other cells of the body of their child.

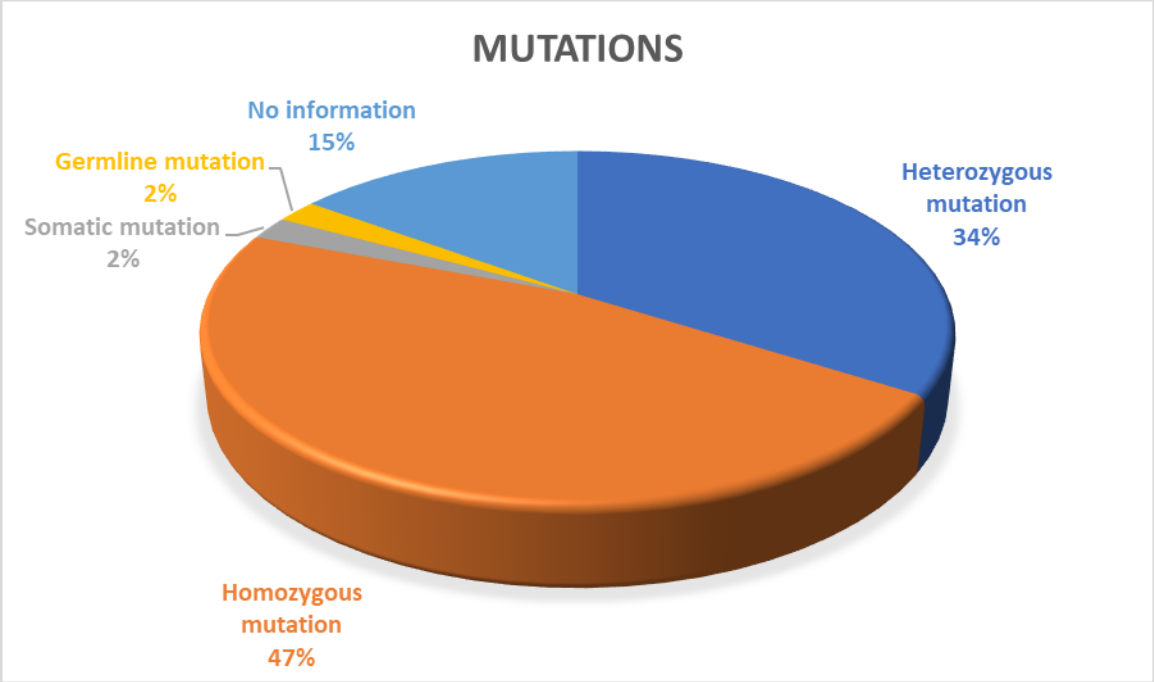

Fig 4.3: Types of mutations in bHLH-associated diseases.

- **Chromosomes:**

Fig 4.4 shows the chromosomal locations where these mutations happen. It shows the result of the specific chromosomes that are being mutated and create disorders. The chart says, chromosome 2 is the highest mutated chromosome that create diseases, whereas chromosome 11, 12, 13, 14 and 16 are the lowest mutated chromosomes. Each of the color are showing different ranges of the chromosomes that are affected during mutation. In the bottom portion of the pie chart, the chromosome number with their respective colors are given.

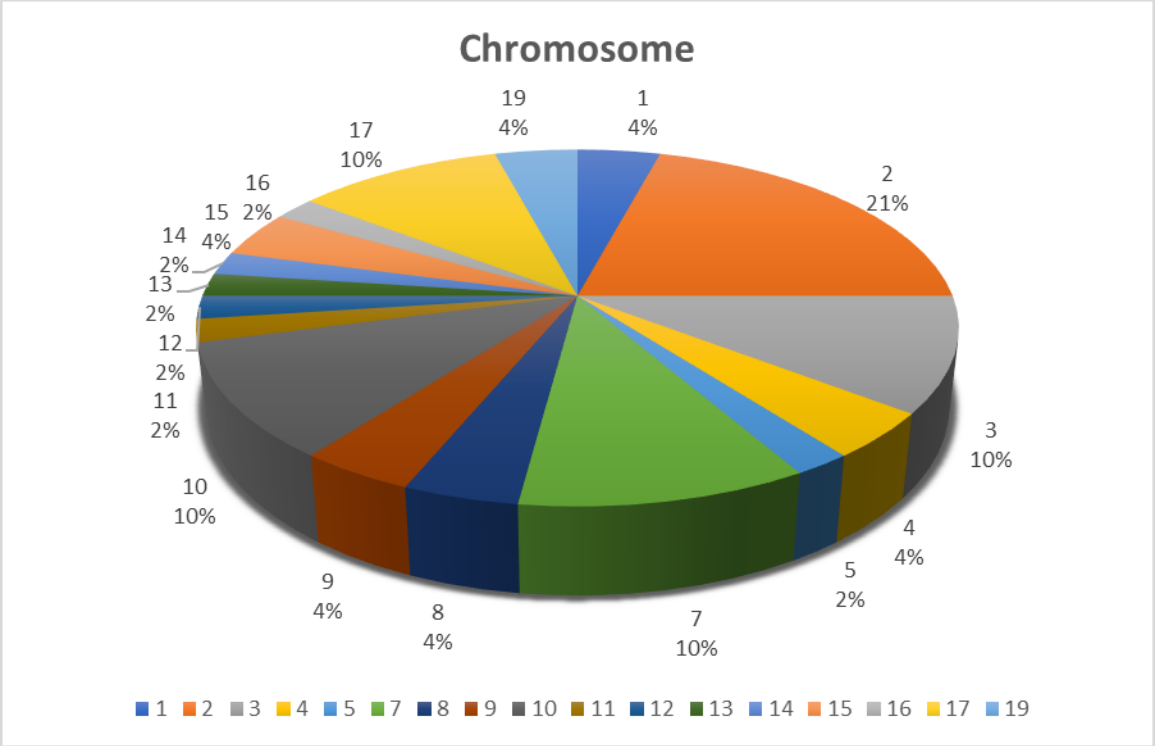

Fig 4.4: Chromosomal locations of bHLH associated diseases.

- **Symptoms:**

Fig 4.5 identifies the major symptoms when the disorders attack patients. Skin and Epithelial system shows the highest symptoms, the Sensory system shows the 2nd highest symptoms, Nervous system shows the 3rd highest result, Skeletal system shows the 4th highest result, Cardiac system shows the 5th highest result, Circulatory system shows the 6th highest result, Renal system shows the 7th result, Gastrointestinal and the Reproductive systems shows the same range and got 8th highest result, Respiratory system shows the 9th highest result, Endocrine system shows the 10th highest result and the cancer shows the lowest result. Symptoms of 15 disorders are being shown by Sensory system, 14 disorders show symptoms through Nervous system, Respiratory system shows symptoms of 2 disorders, Circulatory system related symptoms are seen in 6 disorders, 16 disorders show symptoms by Skin and Epithelial system, Reproductive system related symptoms are seen in 4 diseases, 13 disorders show symptoms through Skeletal system organs, Muscular system related organs show symptoms in only 4 disorders, Endocrine system defects are seen in 3 diseases, Cardiac system symptoms are seen in 7 disorders, Gastrointestinal

system related symptoms are seen in 4 disorders, Renal system defects are seen in 5 syndromes, Cancer are seen least in as syndrome's symptoms, only in 1 disease. Others symptoms are seen in 6 disorders.

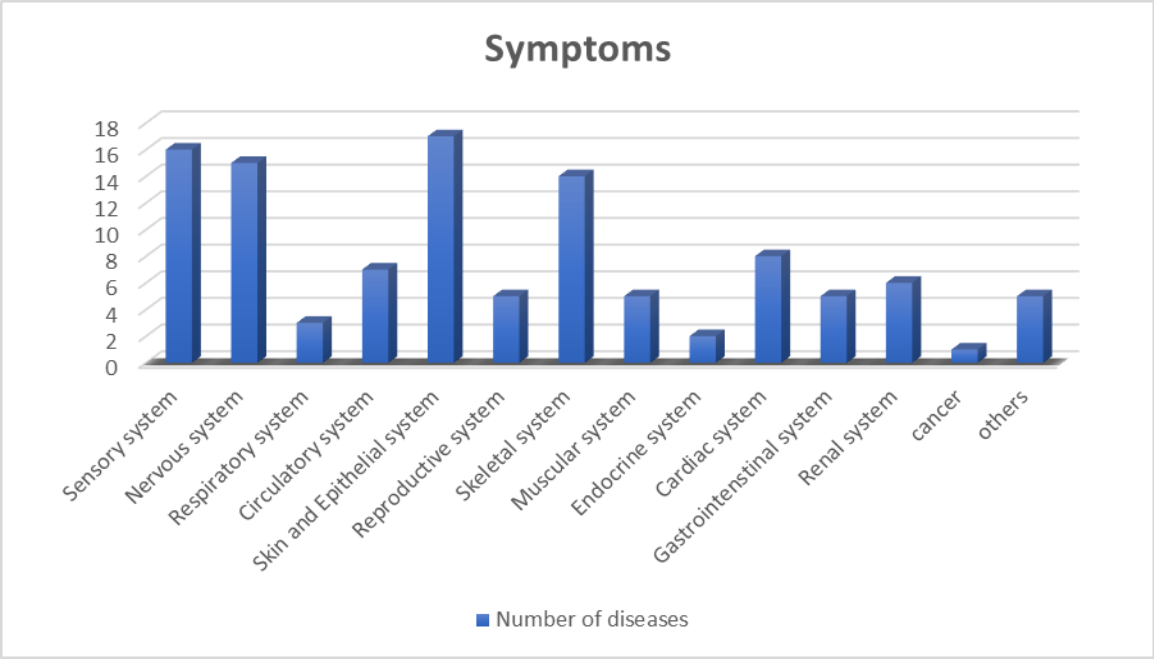

Fig 4.5: Distribution of Symptoms in bHLH-associated diseases

5. Diseases caused by bHLH protein mutations

Mutations on bHLH proteins can cause several disorders. bHLH protein is an essential part of Transcriptional factors. During transcription process those mutations attacks and create diseases. In this portion a detail of those diseases that are caused by the mutations in bHLH protein during transcription process are briefly discussed. Gene name, Protein name and Inheritances are given as sub-points before every disorder description.

5.1. Disease 01

Disease name: Retinitis Pigmentosa 85 (RP85)

- Gene name: AHR
- Protein name: Aryl Hydrocarbon Receptor
- Inheritance: Autosomal Recessive

Retinitis Pigmentosa 85 (RP85) is consistent with Autosomal Recessive inheritance. Based on a report of a family in India, 2 distantly related boys were found that have 2 patients of this disease. This disease is a type of Retinitis Pigmentosa disease. This disorder is a retinal dystrophy and belongs to the group of Retinitis Pigmentosa. The disease is expressed by the primary loss of rod photoreceptor cells (Fig 5.1). These cells are followed by secondary loss of cone photoreceptor. Patients start to lose their primary vision power and gradually loose the central vision. This disorder is forms because of the mutation on AHR gene. This disease is related to some other diseases like: Hemoglobin Lepore-Beta-Thalassemia Syndrome and Middle Lobe Syndrome. The related pathways or super pathways are Innate Immune System. Its response to elevate platelet cytosolic Ca2+. The pathways are connected to Retina. The phenotypes are reduced visual acuity and progress to night blindness. This disorder is occurred due to Homozygous or Compound Heterozygous mutation in AHR on chromosome 7p21.1 [70].

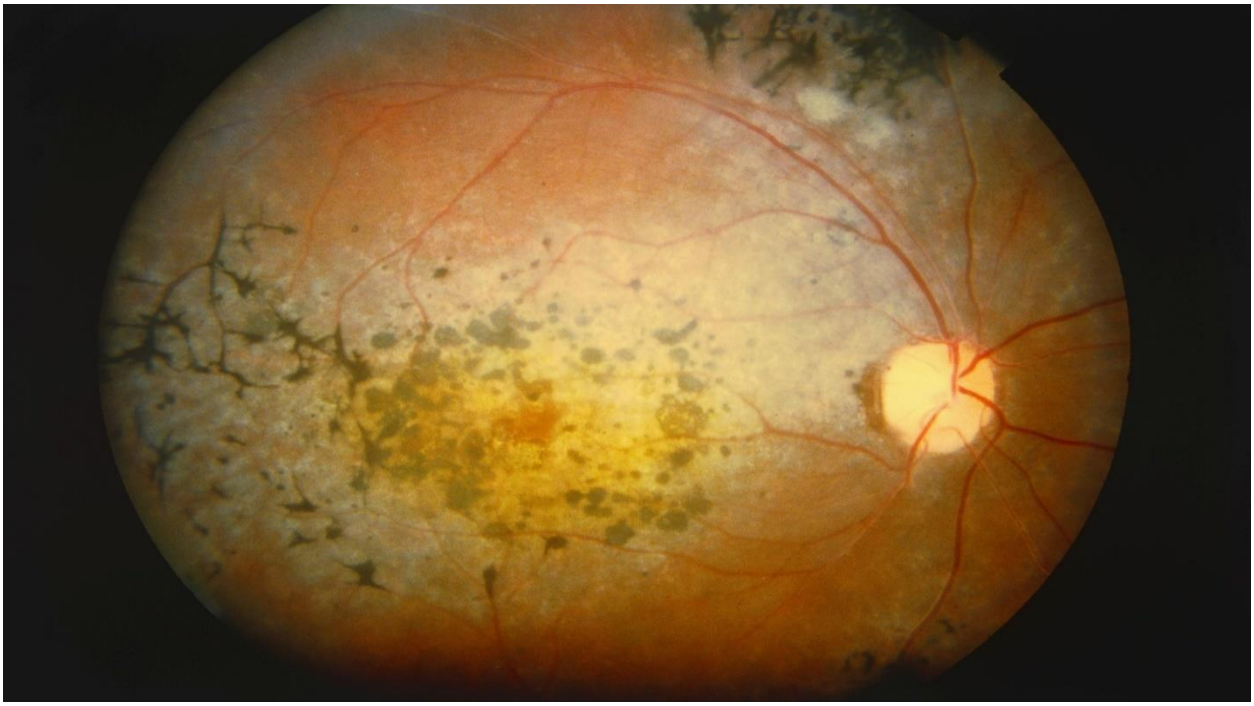

Fig 5.1: Retinitis Pigmentosa 85 (RP85), Adapted from [203]. The figure is showing the hyperpigmentation and a waxy yellow disk surface in the retina of a Retinitis Pigmentosa 85 (RP85) patient.

5.2. Disease 02

Disease name: Webb-Dattani Syndrome (WEDAS)

- Gene name: ARNT2
- Protein name: Aryl Hydrocarbon Receptor Nuclear Translocator 2
- Inheritance: Autosomal Recessive

Webb Dattani Syndrome (WEDAS) an autosomal recessive disorder. This disease is also called Hypothalamo-Pituitary-Frontotemporal-Hypoplasia with Visual and Renal Anomalies. This disorder is specified by Frontotemporal Hypoplasia (Fig 5.2), globally delayed development, Pituitary and Hypothalamic Insufficiency due to Hypoplastic development of these brain region. One consanguineous Saudi Arabian family has been reported (August 2014). Patients soon after birth have hormonal imbalances. He had multiple pituitary gland hormonal deficiency. Soon after his birth, he developed microcephaly, seizures and spasticity. Some other symptoms are also shown like post

retinal blindness and renal abnormalities. The mutation was found by 2 tests, they are: A combination of Homozygosity mapping and Whole Exome sequencing. The cells that collected from the patients were being examined and found that the mutation resulted in nonsense-mediated mRNA and complete loss of ARNT2 function [71].

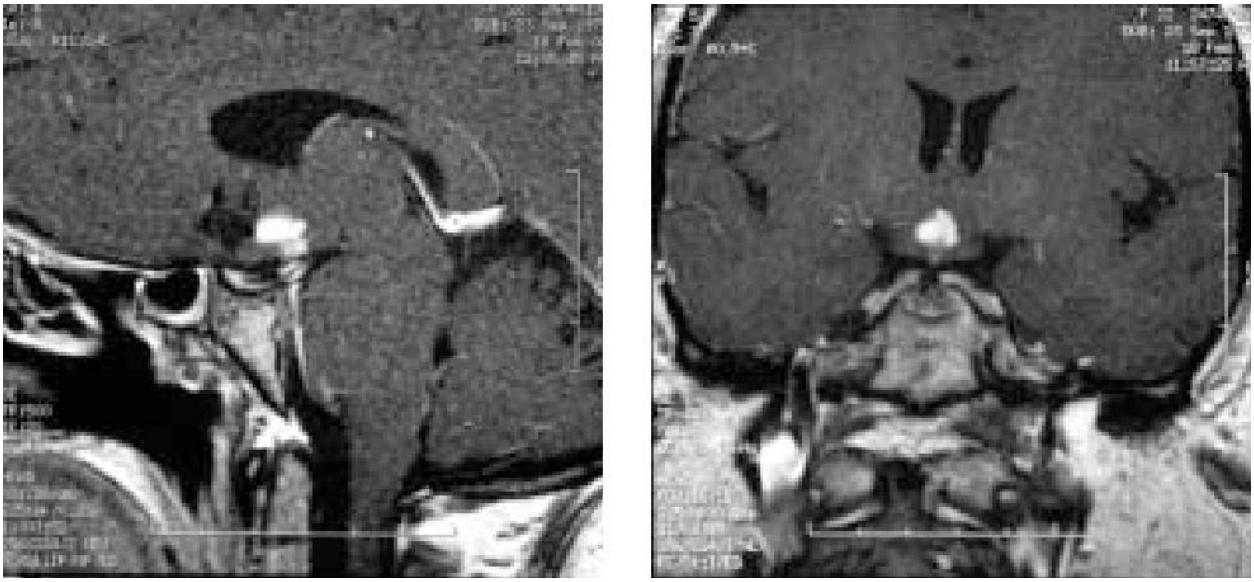

Fig 5.2: MRI report of a Webb-Dattani Syndrome (WEDAS) affected patient, Adapted from [204]

5.3. Disease 03

Disease name: Persistent Hyperplastic Primary Vitreous, Autosomal Recessive (PHPVAR)

- Gene name: ATOH7
- Protein name: Protein Atonal homolog 7
- Inheritance: Autosomal Recessive

Persistent Hyperplastic Primary Vitreous, Autosomal Recessive (PHPVAR) is an autosomal recessive disorder. This disease creates visual deformities. The developmental malformation of the eyes occurs. For that the primary vitreous fails to regress in utero. That is why a retrolental fibrovascular membrane with persistence of the posterior portion of the tunica vascular lentils and hyaloid artery appears and create visual problems (Fig 5.3). Microphthalmia, Cataract, Glaucoma and Congenital Retinal Nonattachment are

associated with this disorder. ATOH gene mutation is responsible for this disorder. Eye, Retina and Bone are affected tissue by the mutation. This disorder is caused by the Homozygous mutation in ATOH7 gene on chromosome 10q21. Related phenotypes of this disease are Iris Coloboma and Uveitis. Moreover, Homozygous deletion in the regulatory region of the ATOH7 gene can be also responsible for this disorder [72, 73, 74, 75].

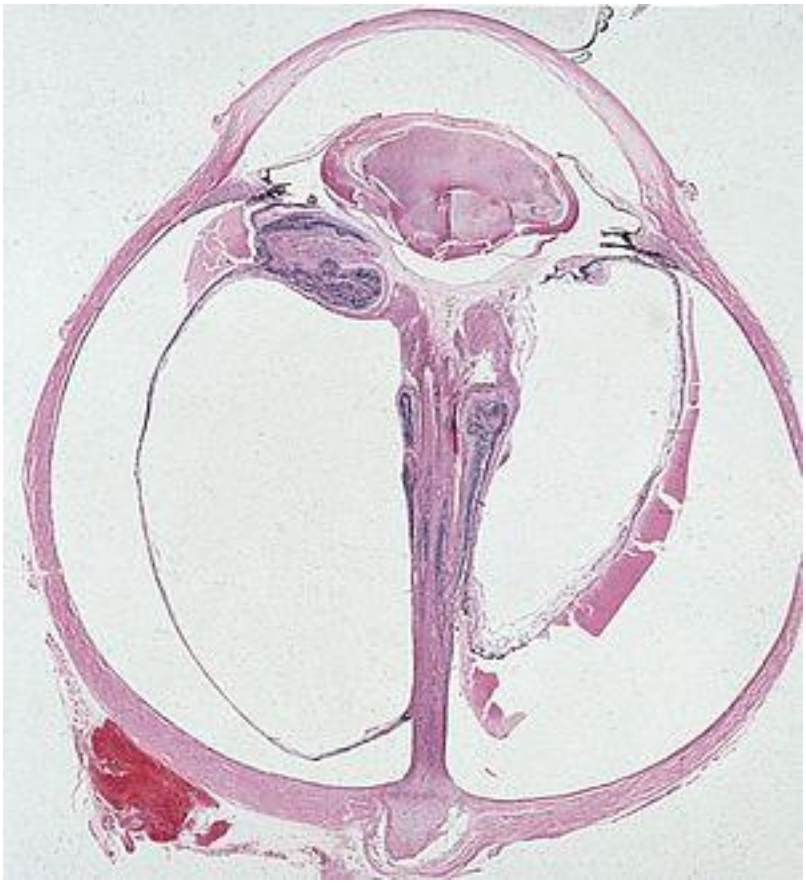

Fig 5.3: Persistent hyperplastic primary vitreous, autosomal recessive (PHPVAR), Adapted from [205]. The figure is showing the eye ball structure and the falciform fold of detached dysplastic retina encircles. The persistence hyaloid artery of the eye of a patient extends from the optic nerve to the retrolental mass.

5.4. Disease 04

Disease name: Split Hand/Foot malformation with long bone deficiency 3 (SHFLD3)

- Gene name: bHLHA9
- Protein name: Class A Basic-Helix-Loop-Helix protein 9
- Inheritance: Autosomal Dominant

Split Hand / Foot malformation with ling bone deficiency 3 (SHFLD3) is an Autosomal Dominant disorder. It is a birth disease which consists of missing finger and/or tor. A deep cleft down the center of the hand and/or foot misses and the fusion of remaining digits (Fig 5.4). SHFM has 6 different types. Each are caused by different mutations. SHFM1 has been linked to chromosome 7, chromosome 7 has been mutated. SHFM2 is connected to X chromosome. Moreover, SHFM3 is caused by the mutation or duplication of chromosome 10, at the position of q24. SHFM4 is caused by the mutation in TP63 gene. SHFM5 is connected to chromosome 2 and SHFM6 is caused by the mutation on WNT10B gene. This disordered is featured by the combination of symmetric severe limb reduction deficiencies. It affects all our 4 limbs, microretrognathia and microstomia [GARD, Malacard, Disease Oncology].

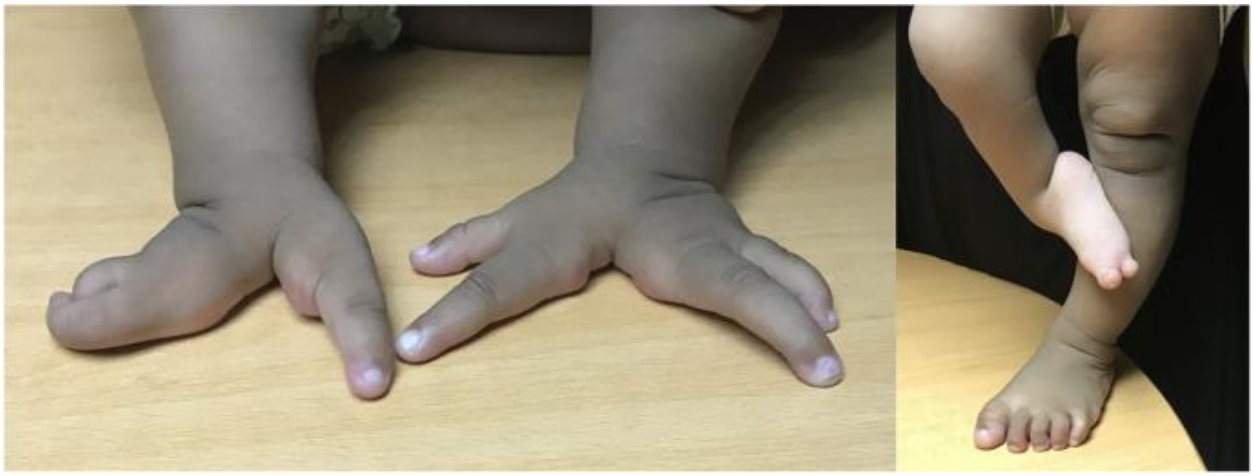

Fig 5.4: Split-hand/foot malformation with long bone deficiency 3 (SHFLD3), Adapted from [206]. The figure shows the malformation of hand and feet of Split hand/foot malformation with long bone deficiency 3 (SHFLD3) patient with missing 3 limbs.

5.5. Disease 05

Disease name: Syndactyly, Mesoaxial Synostotic with Phalangeal Reduction (MSSD)

- Gene name: bHLHA9
- Protein name: Class A Basic-Helix-Loop-Helix protein 9
- Inheritance: Autosomal Recessive

Mesoaxial Synostotic with Phalangeal Reduction (MSSD) is an Autosomal Recessive disorder. The chances of being affected with this disease is very rare, about 1 person in per 1000000 people throughout the world. Infancy and neonatal are mostly affect with this disease. Feet are unaffected in some patients. Some heterozygotes exhibit a mild phenotype shows cutaneous syndactyly between the 2^{nd} and 3^{rd} toes (Fig 5.5) [76, 77].

Fig 5.5: Syndactyly, Mesoaxial Synostotic, with Phalangeal Reduction (MSSD), Adapted from [207]. The figure is showing the malformation of hand fingers of Syndactyly Mesoaxial Synostotic with Phalangeal Reduction (MSSD) patient.

5.6. Disease 06

Disease name: Camptosynpolydactyly, Complex (CCSPD)

- Gene name: bHLHA9
- Protein name: Class A Basic-Helix-Loop-Helix protein 9
- Inheritance: Autosomal Recessive

Camptosynpolydactyly, Cpmp;ex (CCSPD) is an Autosomal Recessive disorder. It is an Autosomal Recessive disease. Based on a report, 2 patients from a family were confirmed a CCSPD patient. This disease is responsible for hand and foot deformities. The disorder is consisting of digits that arise from the dorsum of hands, Syn and Camptodactyly of some fingers and soft tissues syndactyly of the 1st and 2nd toe and dysplastic nails (Fig 5.6). Camptosynpolydactyly, Complex is known as camptopolydactyly, disorganization type. bHLHA9 gene is responsible for the disease. bHLHA9 gene mutation creates the disease. The location of 17p13 Homozygous mutation bHLHA9 gene is responsible for the disorder. Small nails are phenotype of this disease. The disease has been observed by testing SNP Array Analysis Exome Sequencing and Targeted PCR. The mutation was present in heterozygosity in the first-cousin unaffected parents of the patient [78, 79].

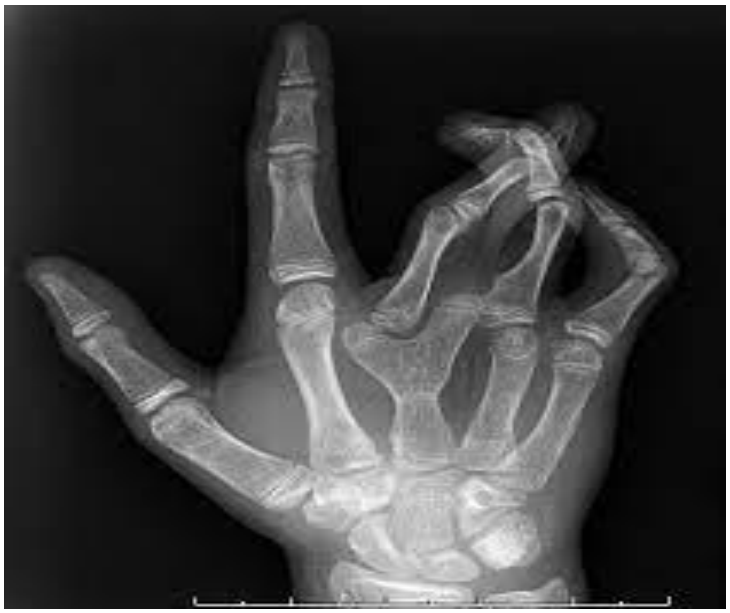

Fig 5.6: Camptosynpolydactyly, Complex (CCSPD), Adapted from [208]. The figure is an X-ray of a Camptosynpolydactyly complex (CCSPD) which is showing the malformation of bones of hands.

5.7. Disease 07

Disease name: Erythrocytosis Familial 4 (ECYT4)

- Gene name: EPAS1
- Protein name: Endothelial PAS domain containing protein 1
- Inheritance: Autosomal Dominant

Erythrocytosis Familial 4 (ECYT4) is and Autosomal Dominant disorder. Often 16-23 years old people are found as patients. Increased serum red blood cell mass and hemoglobin concentration and elevated serum Erythropoietin are the features of this disorder. Mutation in EPAS1 gene is responsible for this disorder. Mutation position is 2p21. The cause of Familial Erythrocytosis 4 (ECYT4) is the gain of function mutation in the gene HIF2A, position 2q21 [80,81,82].

5.8. Disease 08

Disease name: Premature Ovarian Failure 6 (POF6)

- Gene name: FIGLA
- Protein name: Factor in the Germ line Alpha
- Inheritance: Autosomal Dominant

Premature Ovarian Failure 6 (POF6) is an Autosomal Dominant disorder. The disorder is identified by the cessation of ovarian function under the age of 40. Oligomenorrhea or amenorrhea in the presence of elevated levels of serum gonadotropins and Low Estradiol are the characteristics of the disorder (Fig 5.7). This disease is also known as Folliculogenesis. Specific bHLH Transcription Factor FIGLA gene is associated with this disorder. Polyestradiol Phosphate and Estradiol are approved drugs for this disorder. Both Homozygous and Heterozygous mutations in chromosome 2p13 of gene FIGLA is the cause of POF6 disease. Some patients were found in China that are affected with this disorder. Most of them had menstruation problems in their early teen ager ages and latter had primary amenorrhea. But all of them gave birth to healthy children [83, 84].

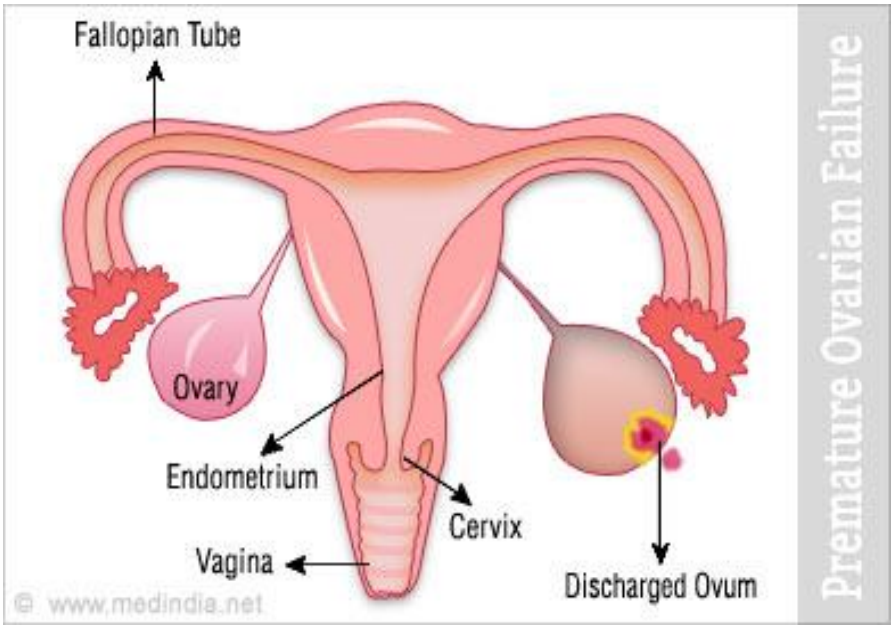

Fig 5.7: Premature ovarian failure 6 (POF6), Adapted from [209]. It shows the Premature Ovarian Failure 6 (POF6), where the discharged ovum is involved in the disturbance of Menstruation cycle.

5.9. Disease 09

Disease name: Spondylocostal dysostosis 4, autosomal recessive

- Gene name: HES7
- Protein name: Transcription Factor HES 7
- Inheritance: Autosomal Recessive

Spondylocostal Dysostosis 4 is an Autosomal Recessive disorder. Spondylocostal dysostosis 4 is a rare type of disease. The characteristics of this disease are Vertebral and Costal Anomalies. Moreover, dwarfism, Vertebral Fusion, Hemivertebrae, Posterior Rib Fusion, Reduced Rib number and Rib Malformation are also some features of this disorder (Fig 5.8). This disorder also known as scdo4 and related to Spondylocastal Dysostosis 5 disorder. HES7 gene and HES Family bHLH Transcription Factor 7 protein is associated with disorder. Homozygous or Compound Heterozygous mutation on the position of 17p13 in the gene HES7 is responsible for the disorder. A Caucasian Mediterranean origin family was found being affected with Spondylocostal Dysostosis (SCDO) where mutation in 3

genes with Recessive SCOD was found. The disorder was identified by performing Autozygosity mapping [Orphannet, Malacards, Gene Reviewer, 85].

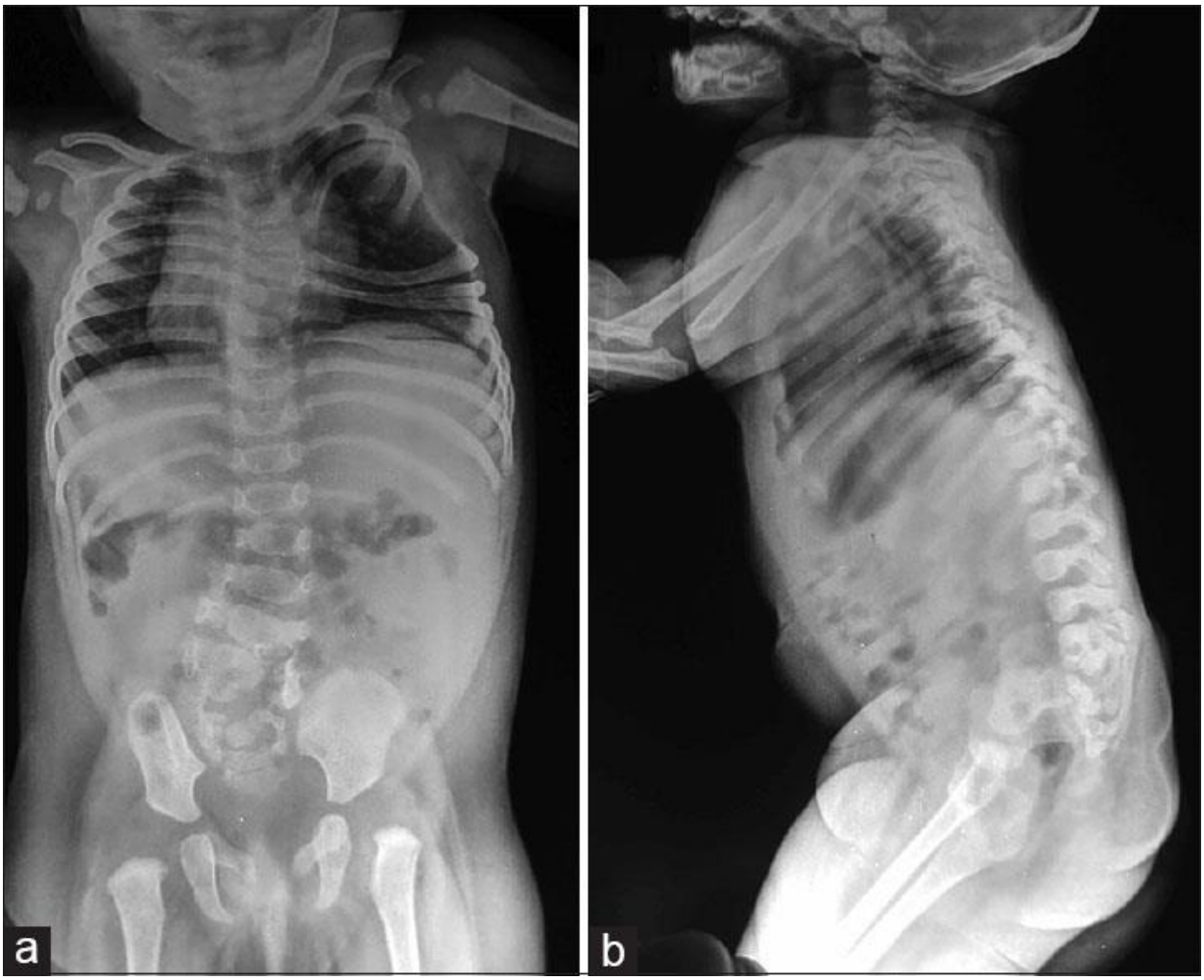

Fig 5.8: Spondylocostal dysostosis 4, autosomal recessive, Adapted from [210].
Radiograph of a Spondylocostal dysostosis 4 child patient showing the deformation of skeleton.

5.10. Disease 10

Disease name: Pheochromocytoma (PCC)

- Gene name: MAX
- Protein name: Protein MAX
- Inheritance: No Information

Pheochromocytoma is a tumor of adrenal gland (Fig 5.9). Adrenal glands are located just above the right kidney. This gland secretes hormones called Epineepinephrines and Norepinephrines. Pheochromocytoma causes the abnormal secretion of those hormones. Too many stresses hormone releasing from the adrenal gland caused by Pheochromocytomas disorder. That is way, High Blood pressure and Headache, Irritability, Sweating, Rapid Heart rate, Nausea, Vomiting, Weight Loss, Weakness, Chest pain and Anxiety symptoms are shown. A type of tumor is it which appears outside the adrenal gland, usually somewhere in the abdomen. This tumor is called Extra-Adrenal Pheochromocytomas or Paragangliomas. In some cases, this disease is called genetic disorder but mostly the reasons are unknown. Some other genes are responsible for this disorder when it does not occur as a part of syndrome. This disorder is also known as Paraganglioma. Symptoms of this disease are: tremor, fever and abdominal pain. TMEM127 gene is assoctiated with this disease. Lenograstim and Ifosfamide are 2 mentioned drugs for this disease [86, 87].

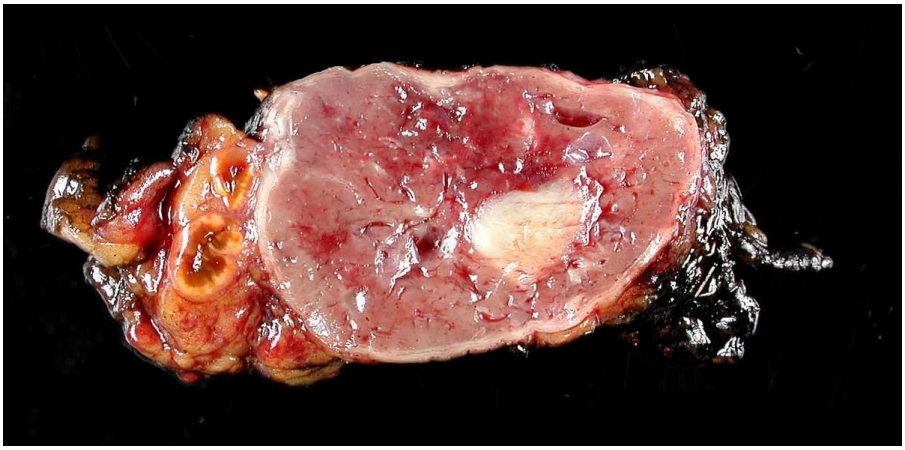

Fig 5.9: Pheochromocytoma (PCC), Adapted from [211]. The figure shows the adjacent normal adrenal gland with Pheochromocytoma (PCC)

5.11. Disease 11

Disease name: Spondylocostal Dysostosis 2, Autosomal Recessive (SCDO2)

- Gene name: MESP2
- Protein name: Mesoderm Posterior Protein
- Inheritance: Autosomal Recessive

Spondylocostal Dysostosis 2 is known as an Autosomal Recessive disorder. Severity of this disorder causes Vertebral and Rib segmentation deformation. Fusion of Vertebrae, hemivertebrae, Fusion of certain ribs, other ribs malformation or deformation Chest spine deformation are some symptoms of this disorder (Fig 5.10). The disorder leads as a result dwarf like appearance. Thorax remains small, as a result respiratory inflammation is very frequently. It is life threatening complication for the new born for the first year of their lives. SCOD2 is another name of this disease. This disorder is related to spondylocostal dysostosis, which is an Autosomal Recessive disease. MESP2 gene and Mesoderm Posterior protein are responsible for this disorder. Related phenotypes are restrictive ventilatory defect and short neck. This disorder is characterized by abnormal vertebral segmentation. Sensorineural hearing loss and Generalized albino like Hypopigmentation on are some characteristics of this disorder. Chromosome 3p13 of gene MESP2 mutation is responsible for this disorder [89, 90].

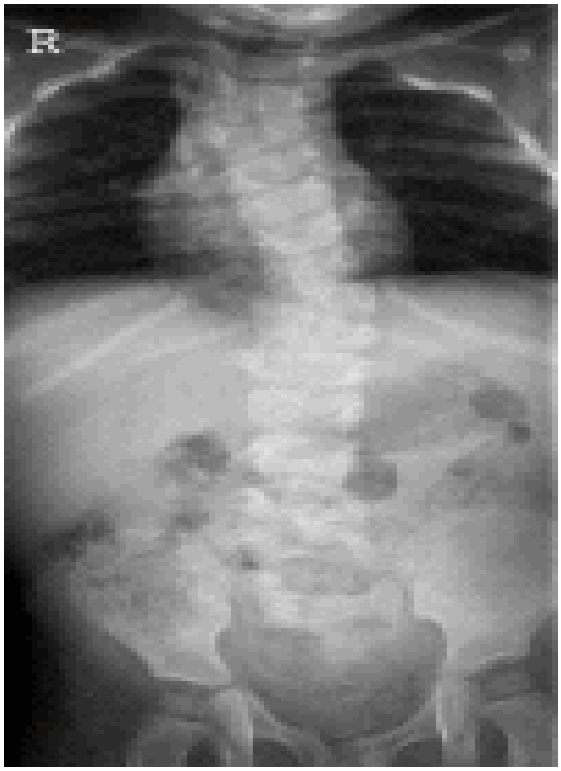

Fig 5.10: Spondylocostal Dysostosis 2, Autosomal Recessive (SCDO2), Adapted from [212]. The figure shows the X-ray result of a Spondylocostal Dysostosis 2 patient with the malformation of skeleton bones.

5.12. Disease 12

Disease name: Waardenburg syndrome 2A (WS2A)

- Gene name: MIFT
- Protein name: Microphthalmia Associated Transcription Factor
- Inheritance: Autosomal Dominant

Waardenburg Syndrome 2A (WS2A) is an Autosomal disorder. It is an Auditory Pigmentary syndrome. Features of this syndrome are: Pigmentary abnormalities of hair, skin and eyes (Fig 5.11), Hearing loss, the absence of Dystopia Cantorum. Dystopia Cantorum is seen in type 2 WS syndrome. WS is also known as Waardenburg Syndrome type 2A, is the member of Waardenburg family. MIFT gene mutation at chromosome 3p13 and protein Microphthalmia associated Transcriptional Factor are associated with this disorder. The frequency rate of Deafness of WD2 is higher than WS1 [91, 92, 93].

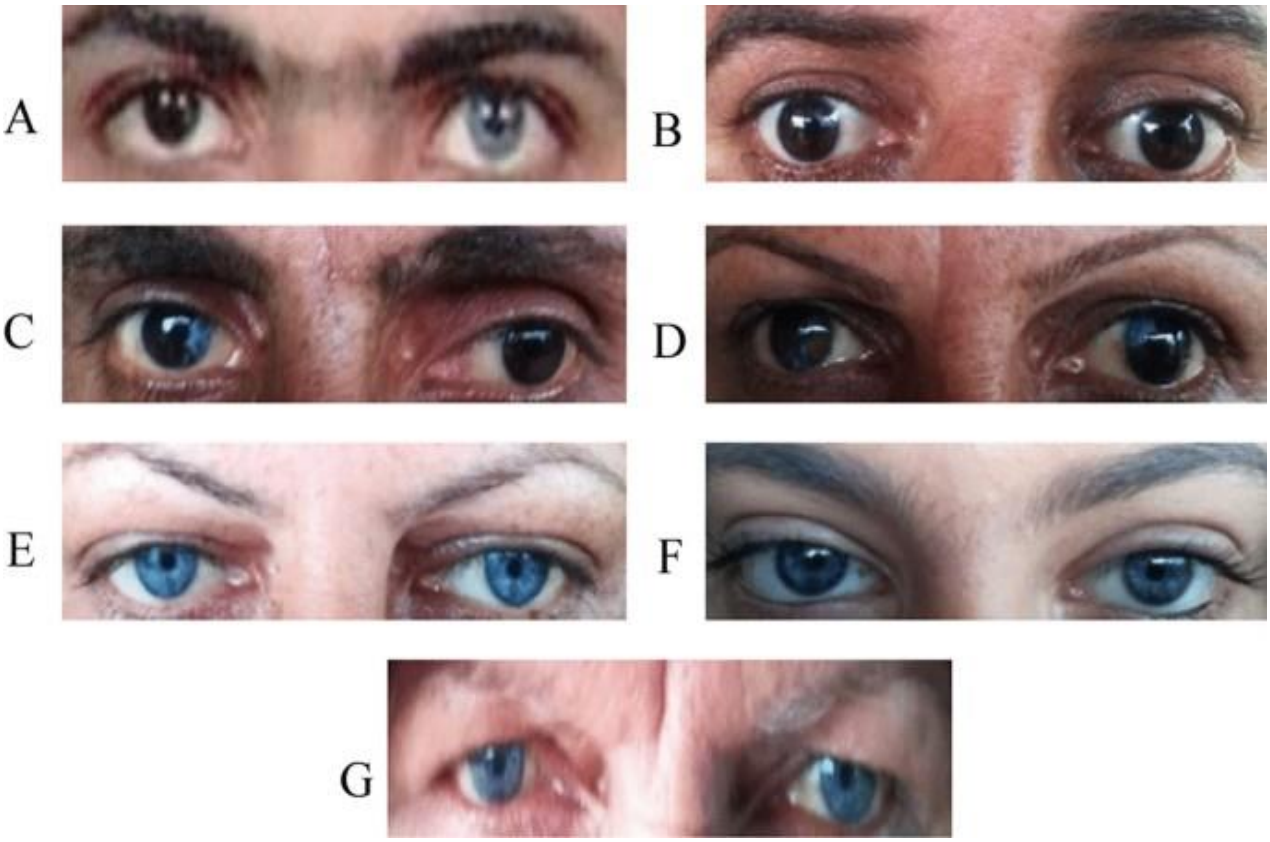

Fig 5.11: Waardenburg syndrome 2A (WS2A), Adapted from [213]. The figure is showing Iris color of type 2A WS2A patients.

5.13. Disease 13

Disease name: Coloboma, Osteopetrosis, Microphthalmia, Macrpcephaly, Albinism and Deafness (COMMAD)

- Gene name: MIFT
- Protein name: Microphthalmia Associated Transcription Factor
- Inheritance: Autosomal Recessive

Coloboma, Osteopetrosis, Microphthalmia, Macrocephaly, Albinism and Deafness (COMMAD) is an Autosomal Recessive disorder. Sever Microphthalmia, Profound Congenital sensorineural Hearing loss, Lack of pigment on the hair skin and eyes (Fig 5.12), Macrocephaly, Facial Dysmorphism and Osteopetrosis are the characters of this disorder. COMMAD syndrome is another name of this disorder. This is related to Tietz Albinism Deafness syndrome and Coloboma of Macula syndromes. MIFT gene mutation on chromosome 3p13 is responsible for this syndrome. Compound Heterozygous mutation is the responsible mutation [94].

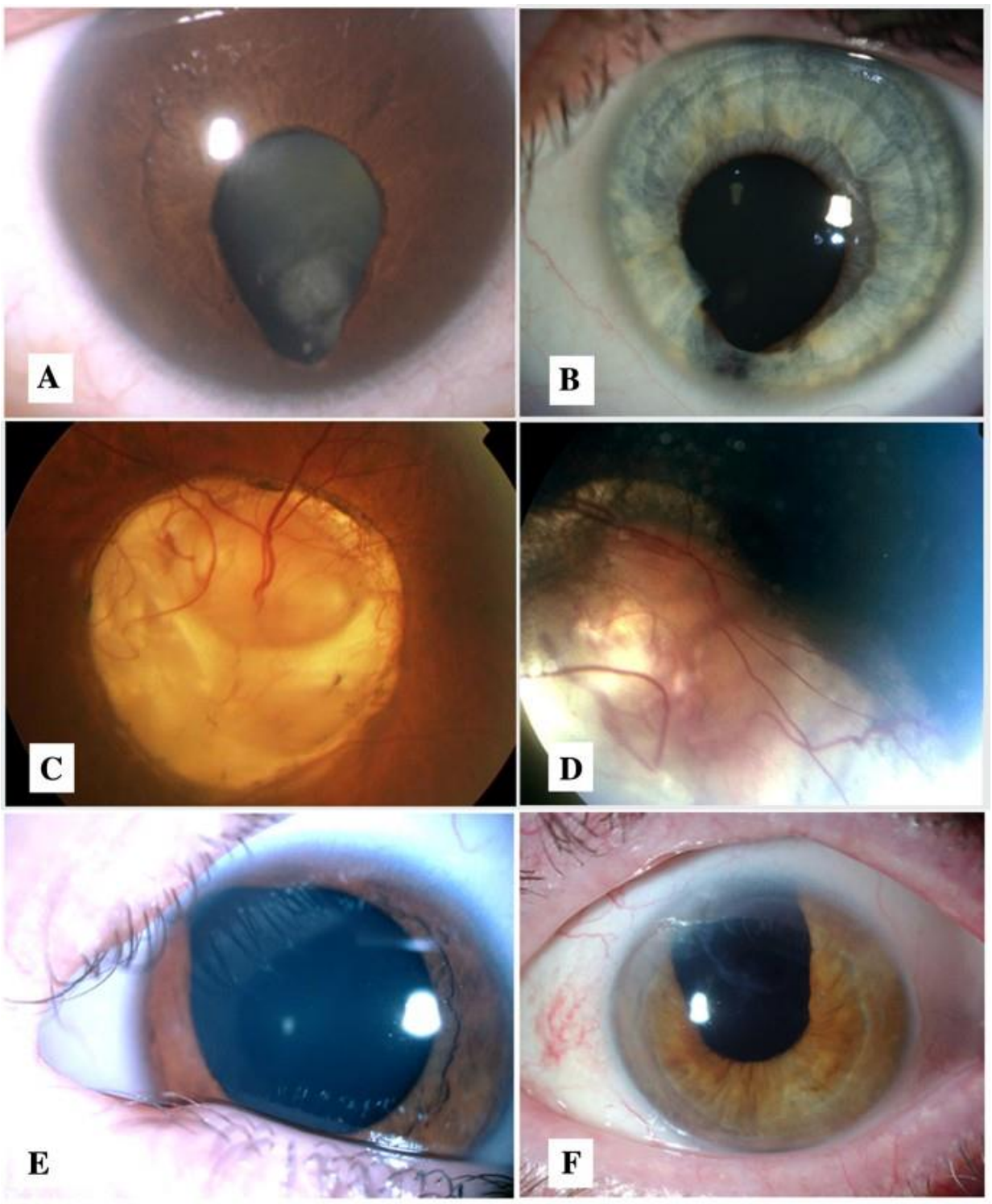

Fig 5.12: Coloboma, Osteopetrosis, Microphthalmia, Macrocephaly, Albinism and Deafness (COMMAD), Adapted from [214]. The figure shows the malformation of Eye lense and retina of COMMAD patients.

5.14. Disease 14

Disease name: Melanoma, cutaneous malignant 8 (CMM8)

- Gene name: MIFT
- Protein name: Microphthalmia Associated Transcription Factor
- Inheritance: No Information

Melanoma, cutaneous malignant 8 is a very rare disease. Melanoma and Renal Cell Carcinoma Predisposition Syndrome has a prevalence of <1/1000000 worldwide. It is and inherited Melanoma and Renal cell carcinoma predisposition cancer syndrome. It occurs due to the Gin of function mutation on the Germline of MIFT gene on chromosome 3p13. Higher incidence of amelanotic and Nodular Melanoma, Multiple primary melanomas and increase in nerve number and size are the features of this disorder. Also known as Cutaneous Malignant Melanoma 8. Nivolumab and Aldesleukin are the mentioned drugs against this disorder. This disorder occurs mostly in skin (Fig 5.13), but also occurs in eye, ears, gastrointestinal tract, leptomeninges and oral and genital membrane [95, 96].

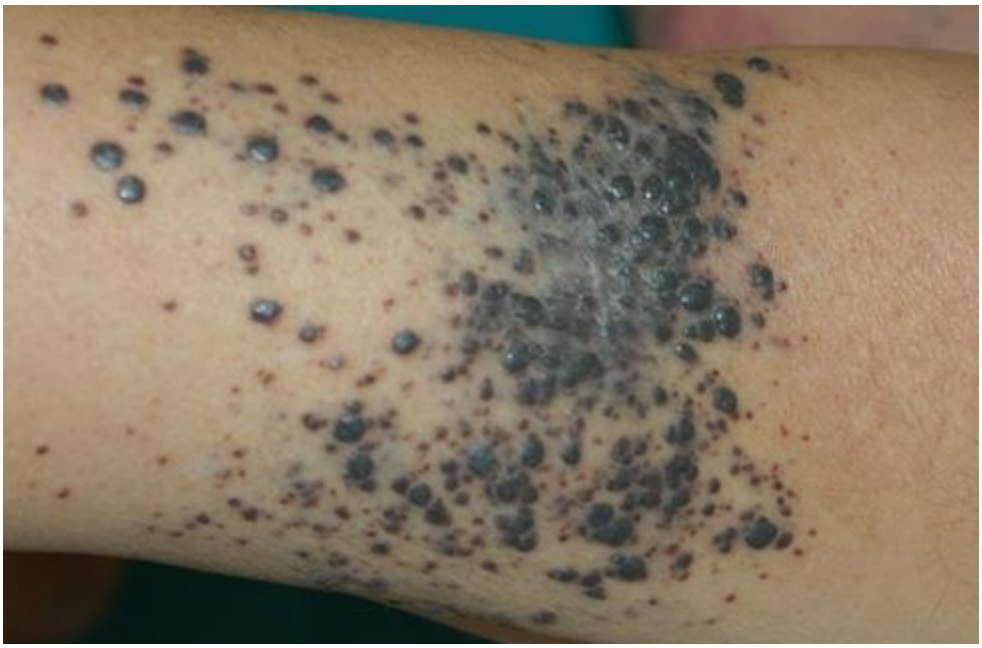

Fig 5.13: Melanoma, cutaneous malignant 8 (CMM8) Adapted from [215]. The illustration of pigmented skin lesions or malignant lesions.

5.15. Disease 15

Disease name: Williams-Beuren Syndrome (WBS)

- Gene name: ELN
- Protein name:
- Inheritance: Autosomal Dominant

Williams Beuren Syndrome (WBS) is an Autosomal Dominant disorder. Possibilities of being affected with this disorder is 1-5/10000 (Worldwide), 1-9/100000 (Europe), 1-5/10000 (Norway), 1-9/100000 (Hong Kong). Antenatal and Neonatal are mostly affect. It is a rare genetic disorder. Characters of this disorder is mild to moderate delays in cognitive development or learning difficulties, defective facial appearance (Fig 5.14) and a unique personality that combines over friendliness and high levels of empathy with anxiety. Most specific phenotype is cardiovascular disease which is caused by narrowed arteries. Deletion of small piece of chromosome 7 is the main cause of the disorder. There is 50% of chance of passing this disorder to children from their parents. Puffiness around the eyes, short nose with broad lips, wide mouth, full checks, full lips and small chin, long neck, sloping shoulder, short stature, limited mobility in their joints and curvature of the spine are the phenotypes of the disorder. Williams Syndrome is another name of Williams Beuren Syndrome. Majority patients of this disorder gets diabetes or pre-diabetes and sensory hearing loss by the age of 30. ELN gene is responsible for this disorder. Dopamine and Buspirone is mentioned for the treatment for this disorder. A Homozygous deletion of 1.5 and 1.8 Mb on the chromosome 7q11.23 which contains ~28 genes is the cause of developing this disorder [97, 98, 99].

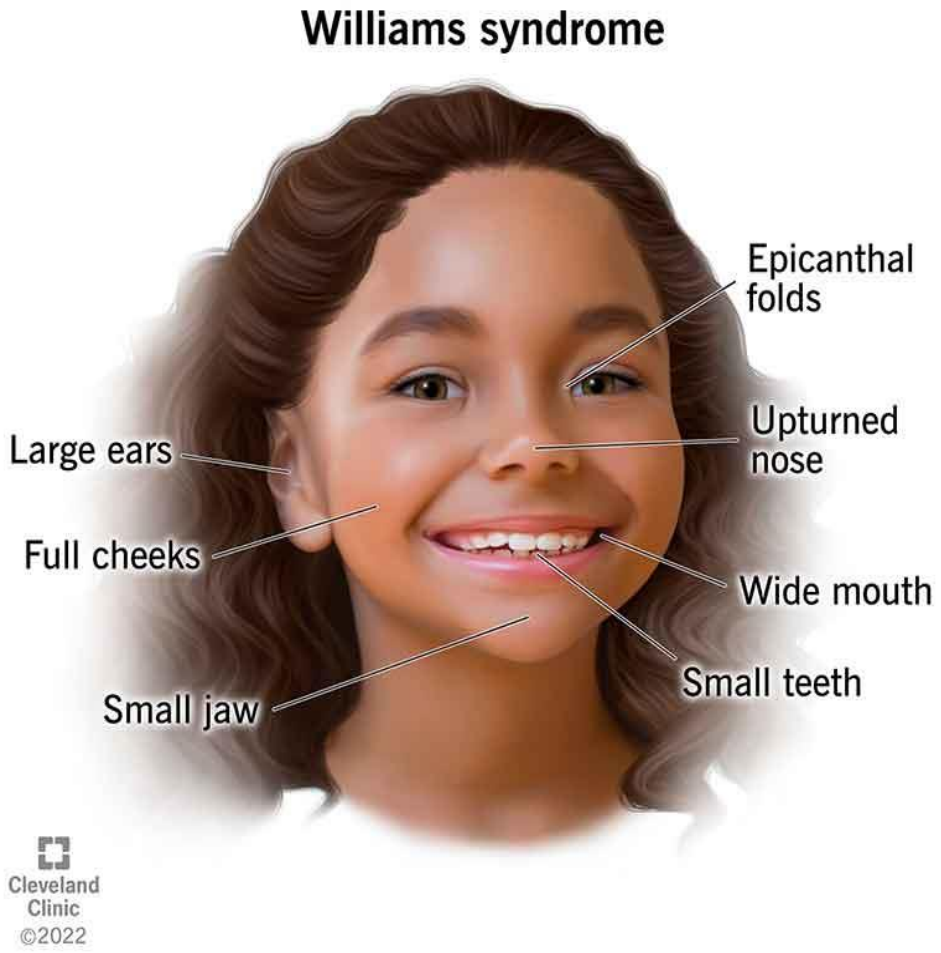

Fig 5.14: Williams-Beuren Syndrome (WBS) Adapted from [216]. The figure is showing the facial characteristics like epicanthal folds in eyes, large ears, upturned nose, full cheek and wide mouth, small teeth and small jaw.

5.16. Disease 16

Disease name: Prostate cancer

- Gene name: CHEK2
- Protein name: Checkpoint Kinase 2
- Inheritance: Somatic mutation

Prostate cancer is a somatic mutation. Possibilities of being affected 1-9/100000 (United States). This is an adult disease. This is a disorder that only affect men. It mostly affects aged men or aged men. At early stage, the central cells become abnormal and start to

multiply without control and form a tumor. Then the tumor turns into cancer if it is not diagnosis. In the early stage of cancer does not show any symptoms, signs or symptoms are shown or very little signs that people do not take seriously. Gradually the tumor increased and symptoms start to show difficulties (Fig 5.15). Pain starts to feel during urine or loss control on urine, blood in urine or semen, feeling of not able to empty bladder completely, pain increase day by day. These are some common symptoms of prostate cancer. Severity is being shown gradually. The early stage of Prostate cancer can be treated. Old patients having Prostate cancer develops so slowly that they do not feel any abnormalities, even without any treatment. It depends on person to person. Prostate cancer can be life threatening if it is not treated. CHEK2 gene mutation is the cause of developing this cancer. Sodium citrate and Levofloxacin have been mentioned for the treatment of this disease. Most prostate cancer patients do not have any family history which is also called Sporadically. Usually this is not a genetic disorder, ~5%-10% patients are believed to be primarily caused and got genetically from parents. Others are spontaneously mutated tumors. Mutations in BRCA1, BRCA2, HOXB13 or several other gene mutations are responsible for Prostate cancer. Based on the family history youngers are recommended for can screening from their early age. The aggressiveness quantitative trait locus has been mapped to chromosome 19q in case of Prostate cancer [100, 101, 102, 103, 104].

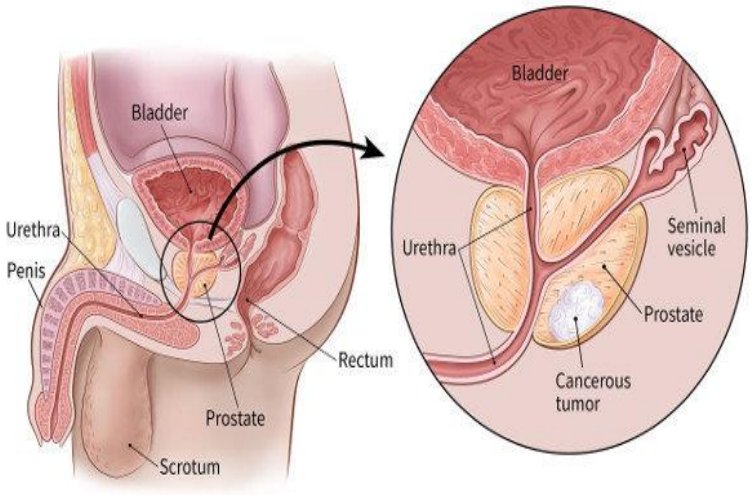

Fig 5.15: Prostate cancer, Adapted from [217]. The figure shows the changes in the prostate after being affected by cancer.

5.17. Disease 17

Disease name: Burkitt Lymphoma (BL)

- Gene name: MYC
- Protein name: MYC Proto Oncogene, bHLH Transcription Factor
- Inheritance: Isolated cases

Burkitt lymphoma is a rare type of disorder where aggressive B-cell produced, which accounts 30% to 50% of lymphoma in children, only 1% to 2% of lymphoma in adults. The inheritance of this disorder is not applicable in websites and it is totally a different case. This disorder is a very fast-growing type of cancer. It forms of B-cell non-Hodgkin's lymphoma (Fig 5.16). It is also known as Burkitt's Lymphoma disorder. The exact reason of this disorder is unknown but it is though that MYC gene and MYV proto-oncogene, bHLH Transcription Factor protein mutation is responsible for this. 3 types of BL have been discovered. For treatment, Intensive Chemotherapy including Chemotherapy to the fluid surrounding the brain and spinal cord is mentioned. Nicotine and clonidine drugs have been mentioned for this disorder. Without timely treatment, BL is rapidly fatal. The pathogenetic mechanisms are not clear still [105,106].

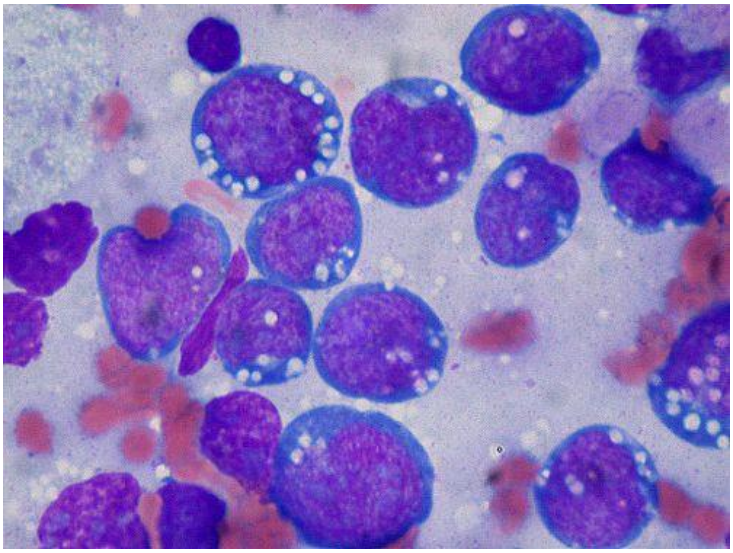

Fig 5.16: Burkitt Lymphoma (BL), Adapted from [218]. The figure shows the growth of Burkitt Lymphoma Cancer cells.

5.18. Disease 18

Disease name: Feingold Syndrome 1 (FGLDS1)

- Gene name: MYNC
- Protein name: MYNC Proto-oncogene Transcription Factor
- Inheritance: Autosomal Dominant

Feingold Syndrome 1 (FGLDS1) is an Autosomal disorder. This is an Autosomal Dominant disorder. It is a very rare disease, prevalence is <1/1000000 worldwide. Antenatal and Neonatal ages are the ages of onset. This is a syndrome that affects whole body. Abnormalities on hands and toes are the characteristics of this disorder. Most of the patients have specific hand abnormalities. This abnormality is called Brachymesophalangy, which means shortening of the 2^{nd} or 5^{th} fingers of hands. Other features are like Underdeveloped thumbs, fusion of 2^{nd} and 3^{rd} toes or the 4^{th} and 5^{th} toes, small hand size, a small jaw, a narrow opening of eyelids, mild to severe learning disabilities, hearing loss, short structure, kidney or heart abnormalities (Fig 5.17). Patients born with Gastrointestinal Atresia which means blockage in a part of their Digestive system. Mostly, the Esophagus or a portion of Small Intestine have the blockage. MYCN gene mutation is responsible for the disease. The protein MYCN Proto-Oncogene, bHLH Transcription Factor protein is responsible and the mutation location is 2p24 number chromosome. It is a Heterozygous mutation [107, 108, 109].

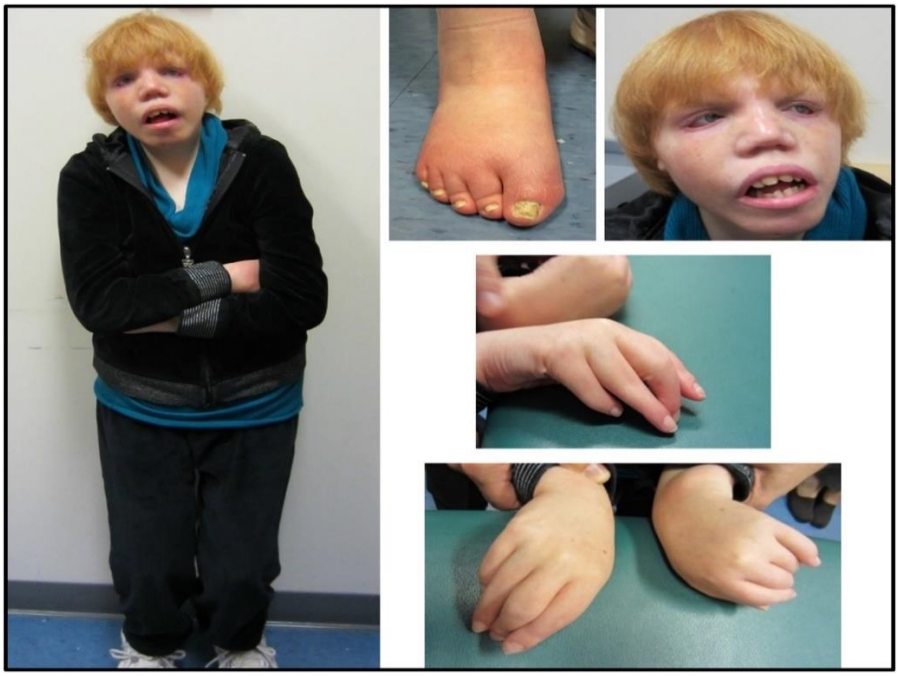

Fig 5.17: Feingold Syndrome 1 (FGLDS1), Adapted from [219]. The figure is showing the malformation of hands of a Feingold Syndrome 1 patient.

5.19. Disease 19

Disease name: Ophthalmoplegia External with Rib and Vertebral Anomalies (EORVA)

- Gene name: MYF5
- Protein name: Myogenic Factor 5
- Inheritance: Autosomal Recessive

Ophthalmoplegia External with Rib and Vertebral Anomalies (EORVA) is an Autosomal Recessive disorder. Also known as Eorva. Some characteristics are: Non-progressive External Ophthalmoplegia and ptosis with Torticollis and Scoliosis development in childhood (Fig 5.18). Patients face Exhibit hypoplastic or missing ribs. MYF5 Homozygous mutation on chromosome 12q21 is responsible for this syndrome [110, 111].

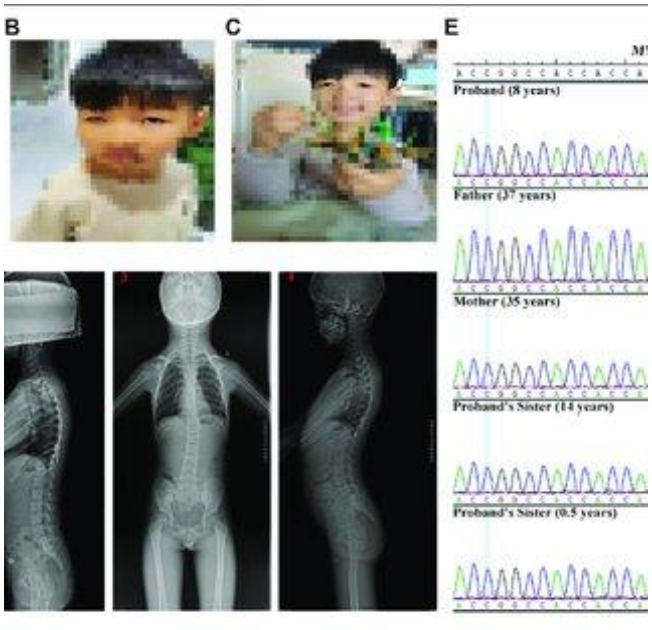

Fig 5.18: Ophthalmoplegia, External, with Rib and Vertebral Anomalies (EORVA), Adapted from [220]. The figure shows the rib deformation of Ophthalmoplegia External with Rib and Vertebral Anomalies (EORVA) patients.

5.20. Disease 20

Disease name: Myopathy Congenital with Diaphragmatic Defects Respiratory Insufficiency and Dysmorphic Facies (MYODRIF)

- Gene name: MYOD1
- Protein name: Myogenic Differentiation 1
- Inheritance: Autosomal Recessive

Myopathy Congenital with Diaphragmatic Defects Respiratory Insufficiency and Dysmorphic (MYODRIF) is an Autosomal Recessive disorder. Highly variable severity and onset in utero. Also known as myopathy, congenital, due to myod1 deficiency. MYOD1 (Myogenic Differentiation 1) gene is associated with this disorder. Poor growth of overall body, Pectus excavatum, Dysmorphic facies and Renal abnormalities are the features of this syndrome (Fig 5.19). Other features like Hypotonia and Respiratory insufficiency associated with High Diaphragmatic dome are also included. Homozygous

mutation of MYOD1 gene on position 11p15 is associated with this disorder [112, 113, 114].

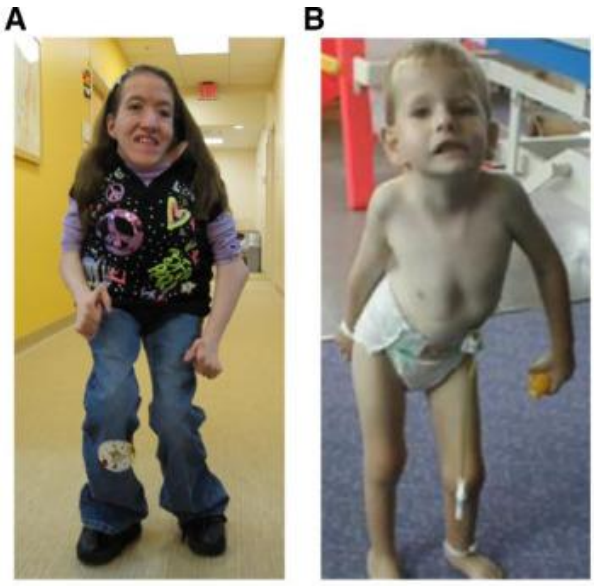

Fig 5.19: Myopathy, Congenital, with Diaphragmatic Defects, Respiratory Insufficiency, and Dysmorphic Facies (MYODRIF), Adapted from [221]. The figure shows the growth disturbance of a MYODRIF patient.

5.21. Disease 21

Disease name: Maturity Onset Diabetes of the Young Type 6 (MODY6)

- Gene name: NEUROD1
- Protein name: Neuronal Differentiation 1
- Inheritance: Autosomal Dominant

Maturity Onset Diabetes of the Young Type 6 (MODY6) is an Autosomal Dominant disease. This disease is basically a type of Diabetes that onsets at very early age, usually before 25 years of age. It is a defect of the secretion of Insulin at the beginning of the disorder. Also known as MODY6. Heterozygous mutation on NEUROD1 gene at position 2q31 is responsible for this disorder [115, 116].

5.22. Disease 22

Disease name: Development and Epileptic Encephalopathy 72 (DEE72)

- Gene name: NEUROD2
- Protein name: Neuronal Differentiation 2
- Inheritance: Autosomal Dominant

Development and Epileptic Encephalopathy 72 (DEE71) is an Autosomal Dominant disorder. Onsets in infancy, variable severity, de novo mutation and two unrelated patients have been reported. It is neurologic disorder. Onset age is around 5 months of age. For treatment, the seizures tend to be refectory. Severely Delayed Psychomotor development, Absence of walking and language skills Hyperkinetic movement, and Cortical visual impairment are the features of this disease. The syndrome is also known as Epileptic Encephalopathy Early Infantile 72 (DEE72). The Heterozygous mutation of NEUROD2 on the chromosome 17q12 is associated with this disease [117, 118].

5.23. Disease 23

Disease name: Diarrhea 4, Malabsorptive, Congenital (DIAR4)

- Gene name: NEUROG3
- Protein name: Neurogenin 3
- Inheritance: Autosomal Recessive

Diarrhea 4, Malabsorptive, Congenital (DIAR4) is an Autosomal Recessive disorder. It is very rare Gastroenterological disease and prevalence is <1/1000000 (Worldwide). Onsets on Infancy and Neonatal period even first weeks of life. A lack of Intestinal Enteroendocrine cells occurs due to a severe Malabsorptive Diarrhea at very early age is the main feature of this disorder (Fig 5.20). This disorder is also known as Enteric Anendocrinosis, is related to neonatal diabetes and diarrhea. NEUROG3 (Neurogenin 3) gene is associated with this disorder. This disease is also known as DIAR4. NEUROG3 gene mutation on the position 10q22 is associated with this disorder [119, 120].

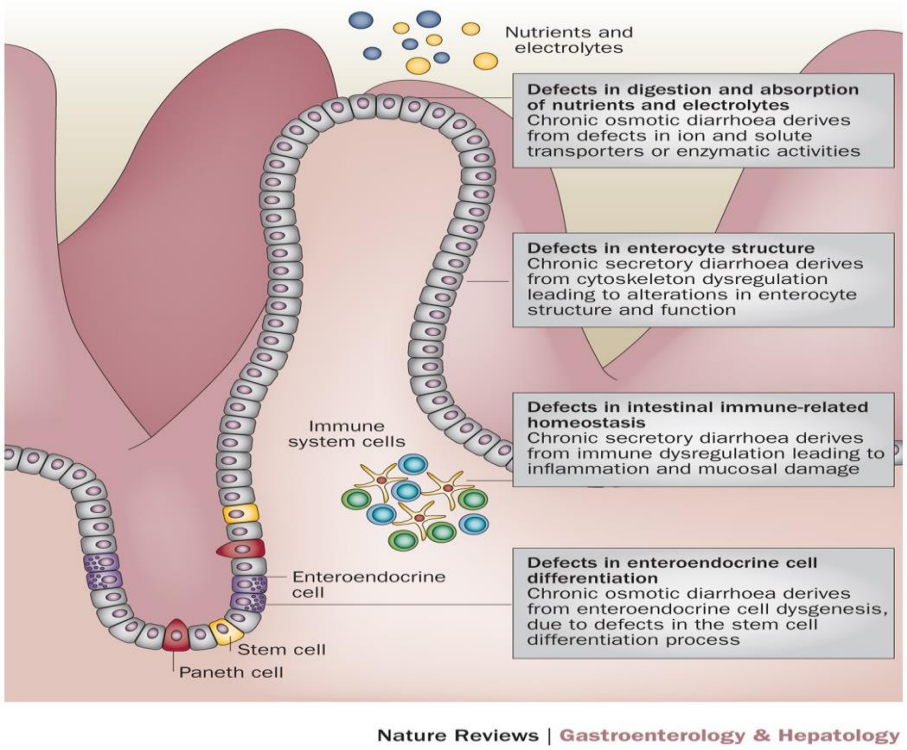

Fig 5.20: Diarrhea 4, Malabsorptive, Congenital (DIAR4), Adapted from [222]. The figure shows the steps of Diarrhea 4 Malabsorptive Congenital (DIAR4) disorder.

5.24. Disease 24

Disease name: Pancreatic and Cerebellar Agenesis (PACA)

- Gene name: PTF1A
- Protein name: Pancreas Associated Transcription Factor 1a
- Inheritance: Autosomal Recessive

This is an Autosomal Recessive disorder. A rare type of disorder with prevalence only <1/1000000 worldwide. Onsets on Infancy, Neonatal period. Usually, people die in infancy stage of life. This is a rare Neurological disease or rare endocrine disease and have developmental abnormalities during Embryogenesis period (Fig 5.21). Neonatal diabetes mellitus, Cerebellar agenesis or Hypoplasia, Severe Intrauterine growth reduction, the presence of very little subcutaneous fat and Dysmorphic facial features are some features of this disorder. This disorder is also known as Mellitus, Permanent Neonatal with

Cerebellar agenesis. Homozygous mutation in PTF1A gene at chromosome 10p12 is associated with disorder [121, 122].

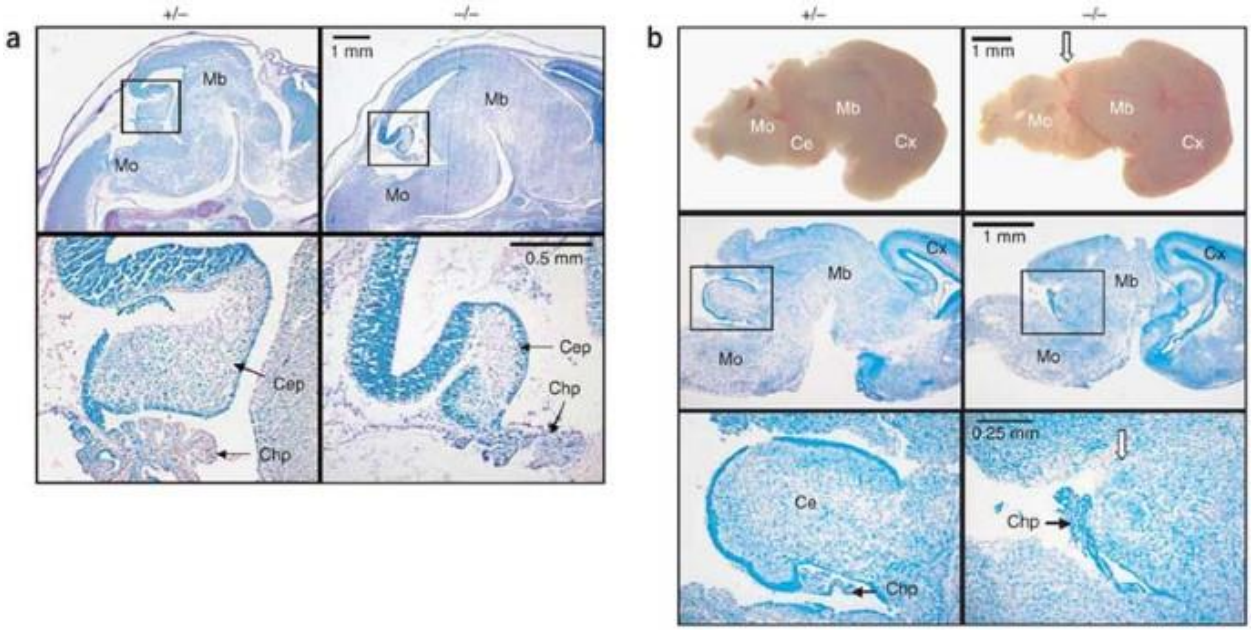

Fig 5.21: Pancreatic and Cerebellar Agenesis (PACA), Adapted from [223]. The figure shows the mutation at PTF1A gene and development of the PACA disorder.

5.25. Disease 25

Disease name: Pancreatic Agenesis 2 (PAGEN2)

- Gene name: PIF1A
- Protein name: Pancreas Associated Transcription Factor 1a
- Inheritance: Autosomal Recessive

Pancreatic Agenesis 2 (PAGEN2) is an Autosomal Recessive disorder. Characters of this disorder are Isolated Hypoplasia or Agenesis of the Pancreas, Pancreatic Beta-cell failure, which as a result creates Neonatal Insulin, Exocrine pancreatic insufficiency (Fig 5.22). This disorder is also known as PAGEN2. Homozygous mutation on PIF1A gen at chromosome 10p12 is associated with this disorder 123, 124].

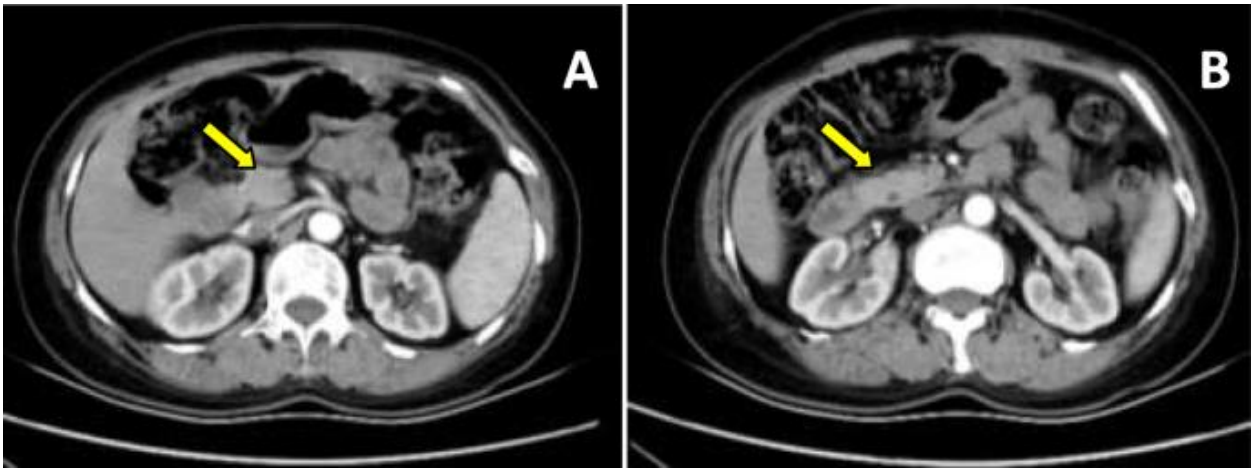

Fig 5.22: Pancreatic Agenesis 2 (PAGEN2), Adapted from [224]. The figure shows the abdominal MRCP which shows a short major pancreatic duct and no visual dorsal duct of a PAGEN2 patient.

5.26. Disease 26

Disease name: Spermatogenic Failure 32 (SPGF32)

- Gene name: SOHLH1
- Protein name: Spermatogenesis and Oogenesis Specific Basic-Helix-Loop-Helix 1
- Inheritance: Autosomal Dominant

Spermatogenic Failure 32 (SPGF32) is an Autosomal Dominant disorder. Male infertility due to nonobstructive azoospermia is the feature of this disorder. Testicular biopsy test result shows the absence of spermatogenic cells and a Sertoli cell only pattern on the report. This disease is also known as SPGF32. Heterozygous mutation on SOHLH1 gene at 9q34 chromosome is associated with the disorder (Fig 5.23) [125, 126].

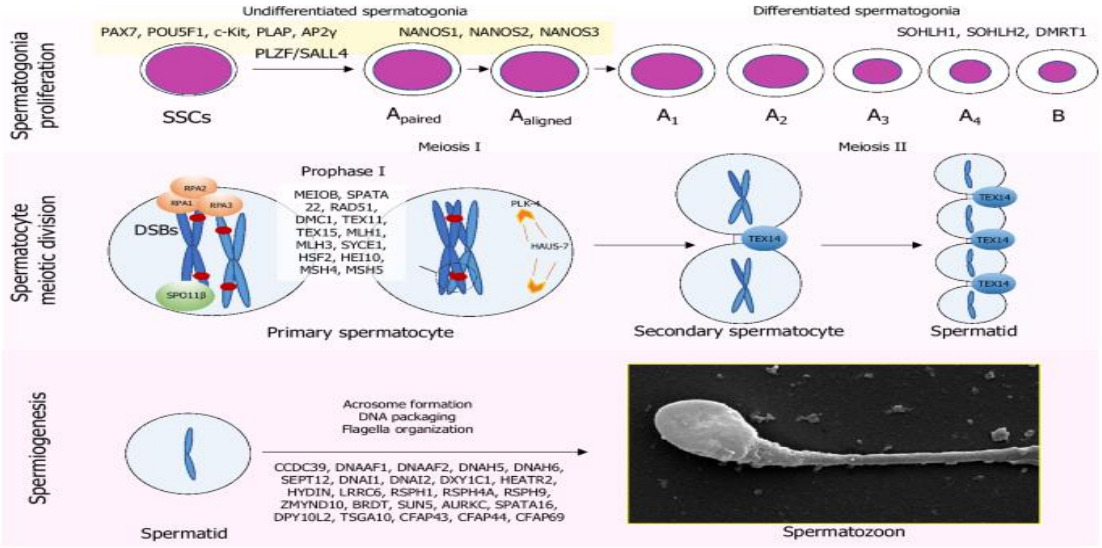

Fig 5.23: Spermatogenic Failure 32 (SPGF32), Adapted from [225]. The figure shows the disturbance of producing sperms of a Spermatogenic Failure 32 patient.

5.27. Disease 27

Disease name: Ovarian Dysgenesis 5 (ODG5)

- Gene name: SOHLH1
- Protein name: Spermatogenesis and Oogenesis Specific Basic-Helix-Loop-Helix 1
- Inheritance: Autosomal Recessive

Ovarian Dysgenesis 5 (ODG5) is an Autosomal Recessive disorder. The disease develops due to the lack of Spontaneous Pubertal development. The features are: Primary Amenorrhea, Uterine Hypoplasia and Hypergonadotropic Hypogonadism. This disorder is also known as ODG5. Homozygous mutation on SOHLH1 gene at chromosome 9q34 is associated with this disorder [127, 128].

5.28. Disease 28

Disease name: Precursors T-cell Acute Lymphoblastic Leukemia (T-ALL)

- Gene name: TLX1
- Protein name: T-cell Leukemia Homeobox 1
- Inheritance: No Information

Precursors T-cell Acute Lymphoblastic Leukemia (T-ALL) is not an Inherited disorder. Adolescent and Adult ages are the onset ages. It is a rare Acute Lymphoblastic Leukemia disorder. A neoplasm of lymphoblasts committed to the T-cell linage, involving bone marrow and blood are the features of this disorder (Fig 5.24). This syndrome is also known as T-ALL. TLX1 gene mutation is associated with this disease. Idarubicin and Vindesine are mentioned drugs of this disorder [129].

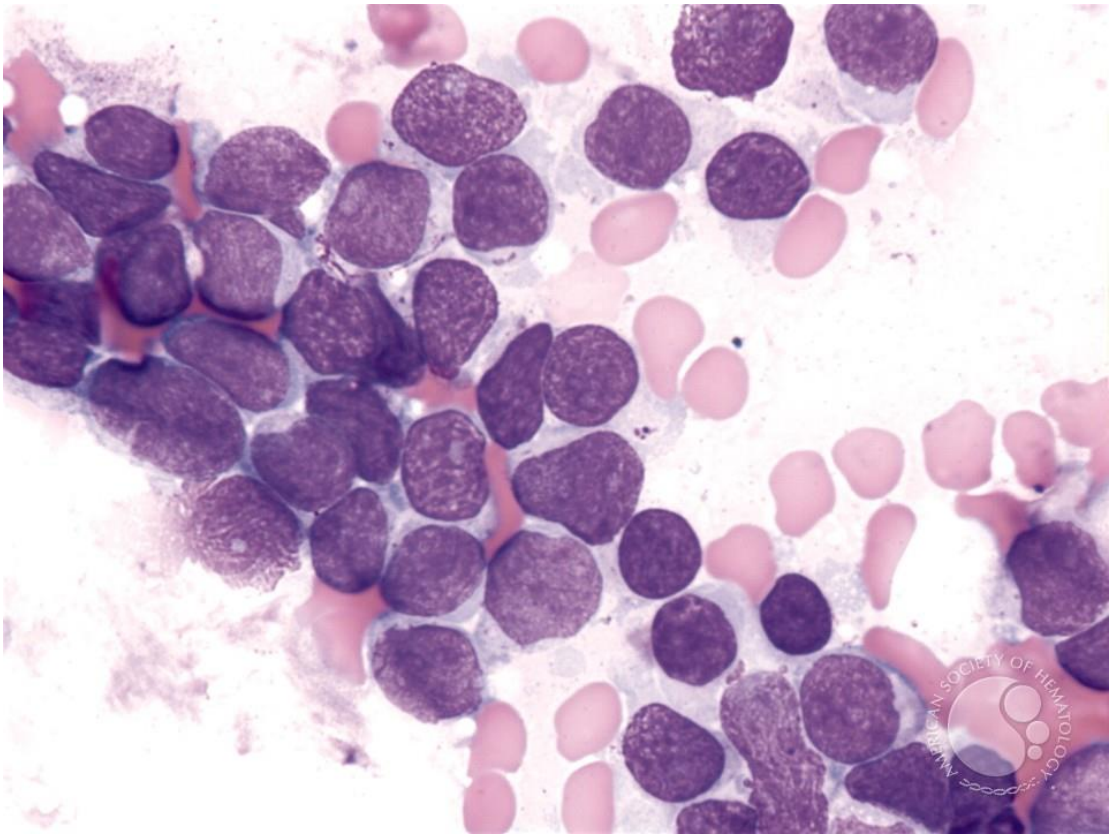

Fig 5.24: Precursor T-Cell Acute Lymphoblastic Leukemia (T-ALL), Adapted from [226]. The figure is showing the development of cancer cells.

5.29. Disease 29

Disease name: T-Cell Acute Lymphoblastic Leukemia

- Gene name: BAX
- Protein name BCL2 Associated X, Apoptosis Regulator
- Inheritance: No Information

T-cell Acute Lymphoblastic Leukemia is a type of Acute Lymphoblastic Leukemia. Too many T-cell Lymphoblasts found in the bone marrow and blood is the characteristics of this disorder (Fig 5.25). This disease is also known as Precursor T-cell Lymphoblastic Leukemia or Lympgoblastic Lymphoma. BAX gene mutation is the cause of this disease. Dexrazoxane and Azathioprine drugs are mentioned for this disease [Malacards].

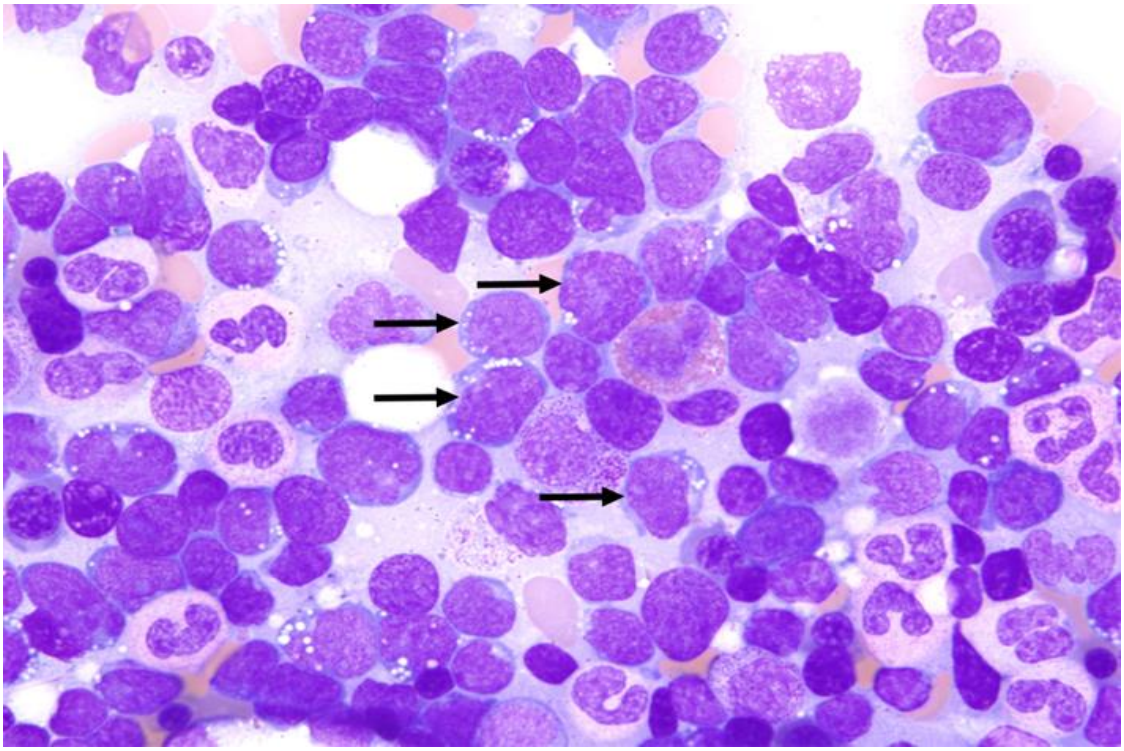

Fig 5.25: T-Cell Acute Lymphoblastic Leukemia, Adapted from [227]. The figure shows the development of cancer cells of a T-Cell Acute Lymphoblastic Leukemia patient.

5.30. Disease 30

Disease name: Craniosynostosis 3 (CRS3)

- Gene name: TCF12
- Protein name: Transcription Factor 12
- Inheritance: Autosomal Dominant

Craniosynostosis 3 (CRS3) is an Autosomal Dominant disorder. It is a disorder where abnormalities are found in skull growth. Premature fusion of the skull growth velocity is the feature of this syndrome, which creates disturbance of developing brain. That is why

skull deformities create intracranial pressure. An abnormal shape of head remains permanently (Fig 5.26). This disorder is also known as CRS3. Heterozygous mutation in TCF12 gene and Transcription Factor 12 at the position of chromosome 15q21 is the cause of this disorder [130, 131].

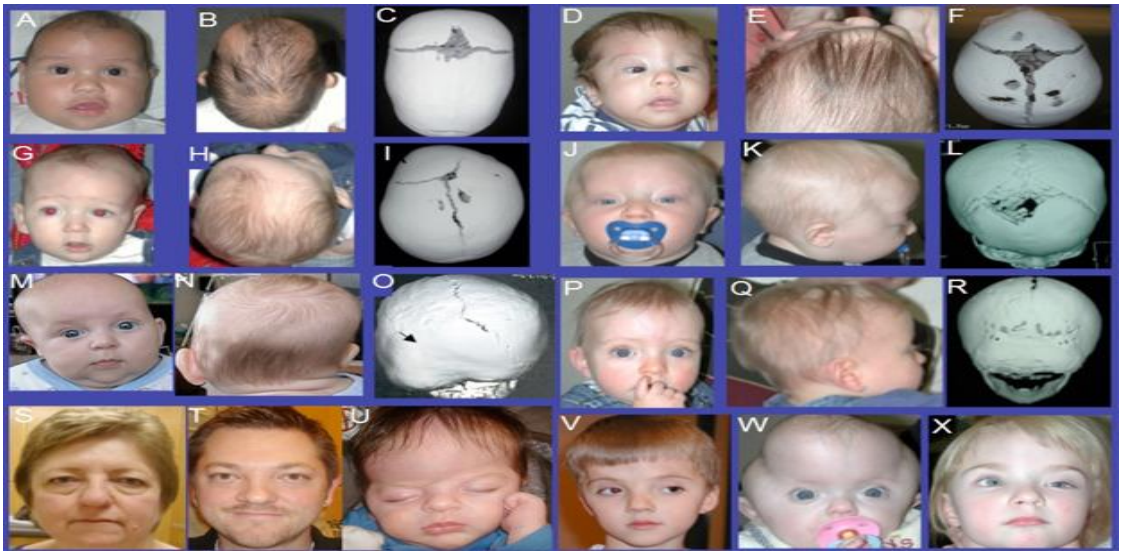

Fig 5.26: Craniosynostosis 3 (CRS3), Adapted from [228]. The figure shows the skull malformations of Craniosynostosis 3 patients.

5.31. Disease 31

Disease name: Agammaglobulinemia 8, Autosomal Dominant (AGM8)

- Gene name: TCF3
- Protein name: Transcription Factor 3
- Inheritance: Autosomal Dominant

Agammaglobulinemia 8 is an Autosomal Dominant disorder. Onsets on Infancy ages. Four unrelated patients have been reported of having de novo mutation. This is a disease of primary immunodeficiency. Characteristics of this disorder are low or absence of serum antibodies and low or absence of circulating B-cell due to an early block B-cell development (Fig 5.27). This disease affects severe infection of patients first year of their life. It is also known as Agammaglobulinemia Autosomal Dominant. Heterozygous

mutation on TCF3 gene and Transcription Factor 3 is responsible for this disorder [132, 133].

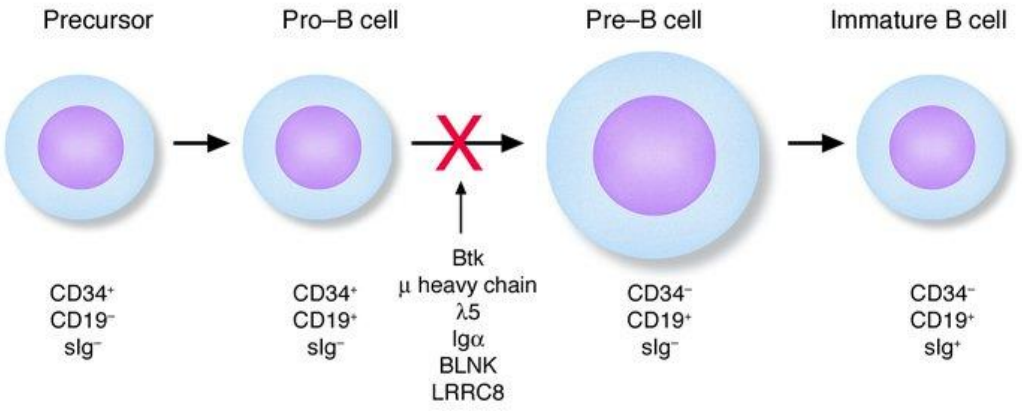

Fig 5.27: Agammaglobulinemia 8, Autosomal Dominant (AGM8), Adapted from [229]. The figure shows the B-cell abnormalities of an AGM8 patient.

5.32. Disease 32

Disease name: Saethre Chotzen Syndrome (SCS)

- Gene name: TWIST1
- Protein name: Twist Family bHLH Transcription Factor 1
- Inheritance: Autosomal Dominant

Saethre Chotzen Syndrome (SCS) is an Autosomal Dominant disorder. It is a rare disorder, prevalence is 1-9/100000 (Europe). Onsets on Antenatal and Neonatal period of life and normal life expectancy. It is a genetic disorder. The characteristic of this disorder is premature fusion of certain skull bone. Prematurely fused skull bone developed of patients along the coronal structure. Other part of the skull malformed as well. The symptoms of the disorder vary very specifically, even individuals of a same family. Some symptoms are: short structure of head, Abnormalities of bones and spine, Hearing loss and Heart defects (Fig 5.28). This disorder is also known as ACS3. Heterozygous mutation of TWIST1 gene at position of 7p21 is associated with this disorder [134, 135, 136, 137].

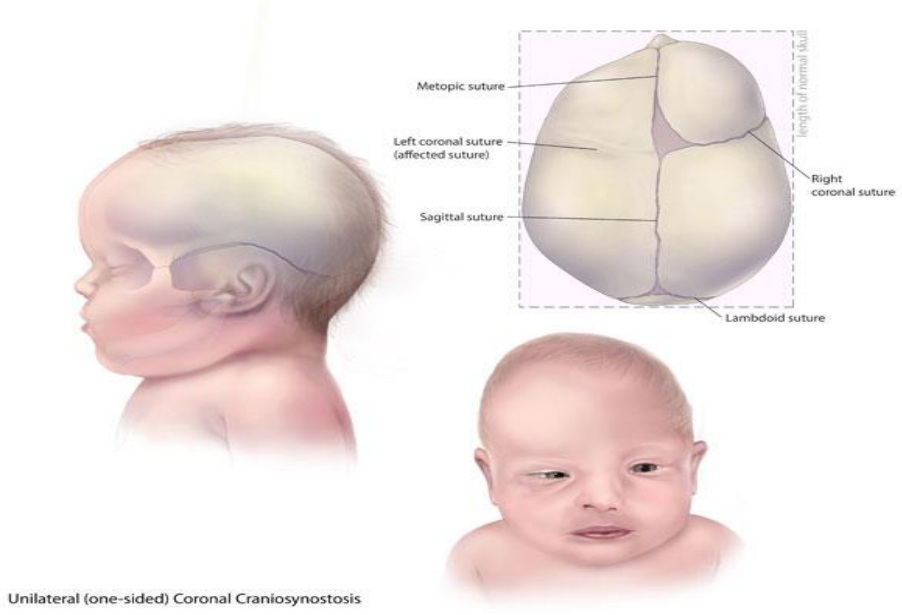

Fig 5.28: Saethre-Chotzen Syndrome (SCS), Adapted from [230]. The figure shows the malformation of skull of a Saethre Chotzen syndrome patient

5.33. Disease 33

Disease name: Robinow Sorauf Syndrome (RSS)

- Gene name: TWIST1
- Protein Name: Twist family bHLH Transcription Factor 1
- Inheritance: Autosomal Dominant

Robinow Sorauf Syndrome (RSS) is an Autosomal Dominant disorder. Some characteristics of this disorder are: Craniosynostosis, Asymmetry of orbits, Flat facts, Hypertelorism, A thin long and pointed nose, great toes with duplication of the distal phalanx (Fig 5.29). RSS and Saethre Chotzin syndrome both disorders are associated with the same gene and clinically bolth are similar. RSS is known as Craniosynostosis Bifid Hallux syndrome. The Heterozygous mutation of TWIST1 gene at the 7p21 chromosome is associated with this disorder [138, 139].

Fig 5.29: Robinow-Sorauf Syndrome (RSS), Adapted from [231]. The figure shows the deformation of hands and skull bone of a Robinow Sorauf syndrome patient

5.34. Disease 34

Disease name: Craniosynostosis 1 (CRS1)

- Gene name: TWIST1
- Protein name: Twist family bHLH Transcription Factor 1
- Inheritance: No Information

Craniosynostosis 1 is not an inherited disease. Rare type disorder, prevalence is only 1-9/1000000 (Worldwide), 1-9/1000000 (France), 1-9/1000000 (Germany), 1-9/1000000 (Italy), 1-9/1000000 (Netherlands), 1-9/1000000 (Austria), 1-9/100000 (Romania), 1-9/1000000 (Spain), <1/1000000 (Turkey). Onsets on Antenatal, Neonatal ages. Ages of death are embryofetal, infantile, stillbirth. It is a birth defect that occur in infant age. It occurs if the mother got infected by the virus during her pregnancy. Rubella virus is the virus that attack pregnant mothers on her 3 months of pregnancy. If the mother got infected with the virus after her 4 months pregnancy, the virus usually does not harm to the baby. Characteristics of this disorder are: Hearing loss, Ocular abnormalities and Heart problem. Some other features are Intrauterine growth retardation, Prematurity, Stillbirth,

Miscarriage, Neurological problems, Liver and spleen problems, Jaundice, Skin problems, Anemia, Hormonal imbalance etc. (Fig 5.30) This disorder is also known as Congenital Rubella syndrome. The heterozygous mutation of TWIST1 gene at the 7p21 is associated with this disorder [140, 141, 142].

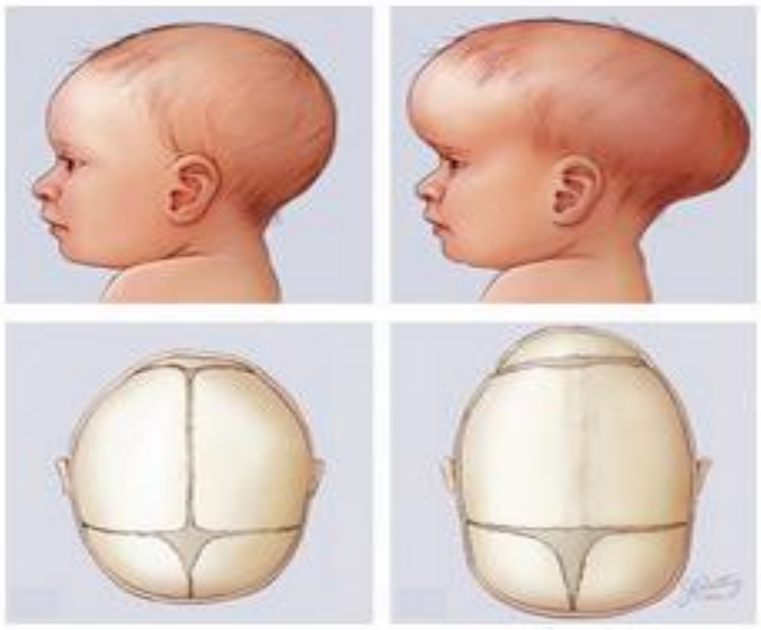

Fig 5.30: Craniosynostosis 1, Adapted from [232]. The figure shows the malformation of skull bone of a Craniosynostosis 1 patient.

5.35. Disease 35

Disease name: Sweeney Cox syndrome (SWCOS)

- Gene name: TWIST1
- Protein name: Twist family bHLH Transcription Factor 2
- Inheritance: Autosomal Dominant

Sweeney Cox Syndrome (SWCOS) an Autosomal Dominant disorder. Some characteristics of the disorder are: Striking facial dysostosis, Hypertelorism, Eyelids and Facial bone deficiencies, low set cupped ears, cleft palate. This syndrome is also known as SWCOS. Heterozygous mutation on TWIST1 at chromosome 7p21 is associated with this disorder [142, 143].

5.36. Disease 36

Disease name: Focal Facial Dermal Dysplasia 3, Setleis Tyoe (FFDD3)

- Gene name: TWIST2
- Protein name: Twist Family bHLH Transcription Factor
- Inheritance: Autosomal Recessive

Focal Facial Dermal Dysplasia 3, Setleis Tyoe (FFDD3) is an Autosomal Recessive disorder. Antenatal and Neonatal ages are the onset ages. It can be life threatening and death can be occurred at any age. It is a rare type of Focal Facial Dermal Dysplasia which is characterized by Congenital Bitemporal Scar like depression and a typical but Variable facial Dysmorphism. Lacking eyelashes, Slanted Eyebrows and bulbous nasal tip, low frontal hairline, redundant skin, low set dysplastic ears etc. (Fig 5.31) This disease is mainly a developmental disorder. This disease is also known as SETLEIS syndrome. Homozygous mutation on TWIST2 gene at chromosome 2q37 is responsible for this disorder [146, 147].

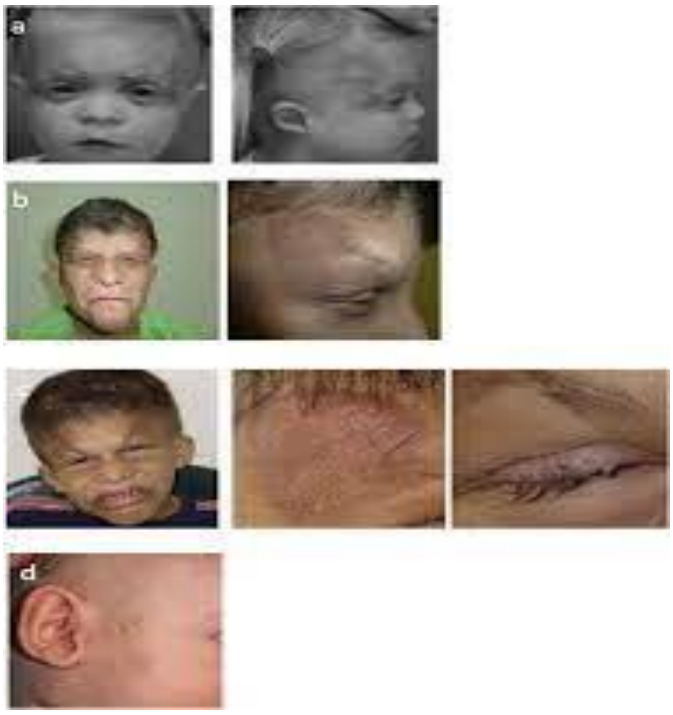

Fig 5.31: Focal Facial Dermal Dysplasia 3, Setleis Type (FFDD3), Adapted from [233]. The figure shows the facial deformations of Focal Facial Dermal Dysplasia 3 patients.

5.37. Disease 37

Disease name: Barber-Say Syndrome (BBRSAY)

- Gene name: TWIST2
- Protein name: TWIST Family Transcription Factor 2
- Inheritance: Autosomal Dominant or Autosomal Recessive

Barber Say Syndrome (BBRSAY), the inheritance of this disorder has been debated. A very rare type disease. Prevalence is only <1/1000000 (Worldwide). Onsets on Neonatal age. Sone characteristics of this disorder are: Excessive hair growth, Papery thin and Fragile skin, Outward turned eyelids, large mouth (Fig 5.32). This disease has no fixed treatment. This disease is also known as Atrophic skin Ectropion and Macrostomia. Heterozygous mutation of TWIST2 gene at chromosome 2q37 is responsible for this disorder [148, 149].

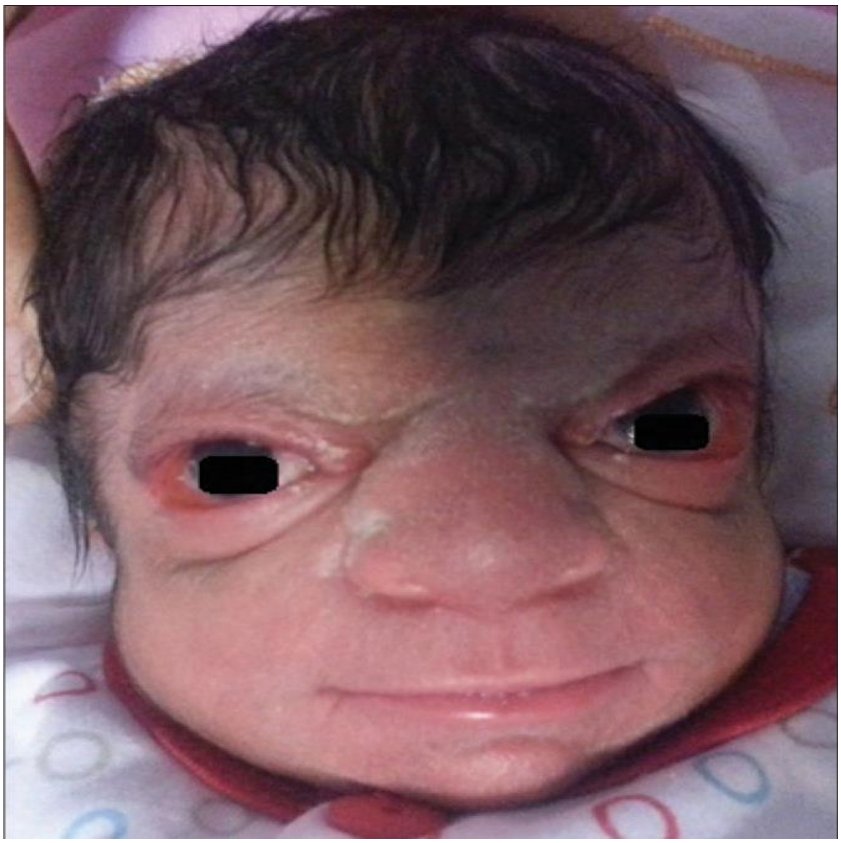

Fig 5.32: Barber-Say Syndrome (BBRSAY), Adapted from [234]. The figure shows the malformation of facial structure of a new born baby patient.

5.38. Disease 38

Disease name: Ablepharon Macrostomia Syndrome (AMS)

- Gene name: TWIST2
- Protein name: Twist Family bHLH Transcription Factor 2
- Inheritance: Autosomal Dominant

Ablepharon Macrostomia Syndrome (AMS) is an Autosomal Dominant disorder. Very rare type disorder, prevalence is only <1/1000000 (Worldwide). Onsets on Antenatal, Neonatal period of life. Absence of eyelids, very large mouth, abnormal external ears, fusion of hands and feet, absence of spare hair, genital malformation and development delay are the features of this disease (Fig 5.33). This disease is also known as Ablepharon Macrostomia syndrome. Heterozygous mutation of TWIST2 gene at 2q37 chromosome is associated with this syndrome. Eye, skin and breast are the affected tissues. Cysteine and Folic acids are used as mentioned drugs for the treatment of this disorder.

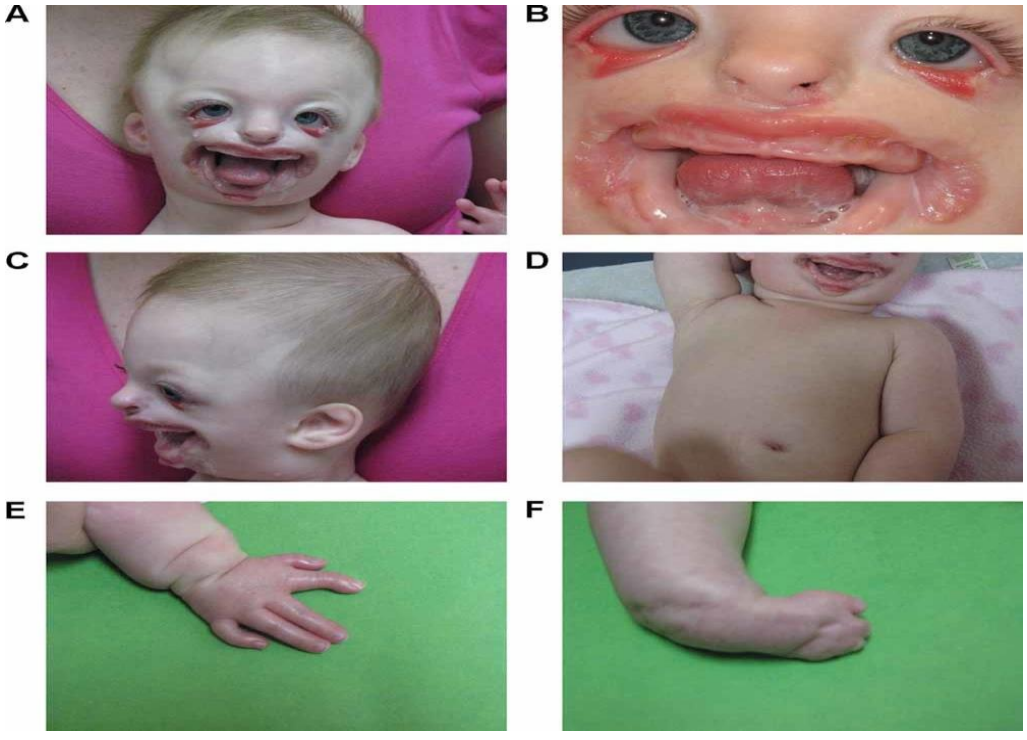

Fig 5.33: Ablepharon-Macrostomia Syndrome (AMS), Adapted from [235]. The figure shows the malformations of face, hands and legs of a Ablepharon Macrostomia syndrome (AMS) patient.

5.39. Disease 39

Disease name: Hyperlipidemia, Familial Combined, 1 (FCHL1)

- Gene name: USF1
- Protein name: Upstream Transcription Factor
- Inheritance: No Information

Hyperlipidemia, Familial Combined 1 (FCHL1) is not an inherited disorder. A visible pattern of elevated levels of serum total cholesterol, triglycerides or both is the symptom of this disease. Patients also faces premature coronary heart disease. This disorder is also known as Hyperlipidemia, Familial combined, Susceptibility disorder. USF1 gene mutation at chromosome 1q23 is associated with this disorder. Heart tissue is the affected tissue. Nicotinamide and Fenofibrate are the mentioned drugs of this disease [154, 155].

5.40. Disease 40

Disease name: Delayed Sleep Phase disorder (DSPD)

- Gene name: CRY1
- Protein name: Cryptochrome Circadian Regulator 1
- Inheritance: Autosomal Dominant

Delayed Sleep Phase Disorder (DSPD) is an Autosomal Dominant disorder. It is a Circadian rhythm sleep disorder. Sleep onset Insomnia, difficulties in awaking at required time are features of this disorder. Patients face chronic problems in balancing sleeping and awaking times. Also known as Delayed Sleep Phase syndrome. This disorder is also related to other sleep related disorders and Major depressive disorders. Heterozygous mutation of CRY1 gene at chromosome 12q23 is associated with this disorder. [156, 157, Malacard].

5.41. Disease 41

Disease name: Central Hypoventilation Syndrome, Congenital, 1 (CCHS1)

- Gene name: PHOX2B
- Protein name: Paired Linked Homeobox 2B
- Inheritance: Autosomal Dominant

Central Hypoventilation Syndrome, Congenital 1 (CCHS1) is an Autosomal dominant disorder. It is a rare disorder. Some characteristics of this disorder are: absence of Neuromuscular, Lund or Cardiac disease, Identifiable brainstem lesion. Patients with cyanosis increase carbon dioxide level of body during sleep in their first hours of lives but become normal when they are awake. This disease is also known as CCHS. Symptoms of this disorder are constipation, dyspnea and hemoptysis. PHOX2B (Paired Like Homeobox 2B) gene is associated with this disorder. Acetazolamide and Opium are mentioned drugs for the treatment. Lung, Heart and Brain are the affected tissues. Heterozygous of the PHOX2B at chromosome 4p13 is associated with this disorder [158,159, Malacard].

5.42. Disease 42

Disease name: Hermansky Pudlak Syndrome 2 (HPS2)

- Gene name: AP3B1
- Protein name: Adaptor related protein complex 3 subunit Beta 1
- Inheritance: Autosomal Recessive

Hermansky Pudlak Syndrome 2 (HPS2) is an Autosomal Recessive disorder. This disorder is a type of Hermansky Pudlak syndrome, which is a multi-system disorder. Characteristics are: Oculocutaneous albinism, Bleeding diathesis and Neutropenia. Patients faces Oculocutaneous albinism, reduced visual acuity, Horizontal nystagmus, Brusing if soft tissues Epistaxis, Prolonged bleeding after dental extraction, problems in surgery or child birth (Fig 5.34). In some cases, Pulmonary Fibrosis has been seen. This disease is also known as HPS2. Symptoms including photophobia and abdominal pain. Homozygous mutation of AP3B1 gene at chromosome 5q14 is associated with this disorder. Pirfenidone and Pravastatin are 2 mentioned drug for the treatment. Skin, B-lymphoblasts and Lung are the affected tissues [160, 161, Malacard].

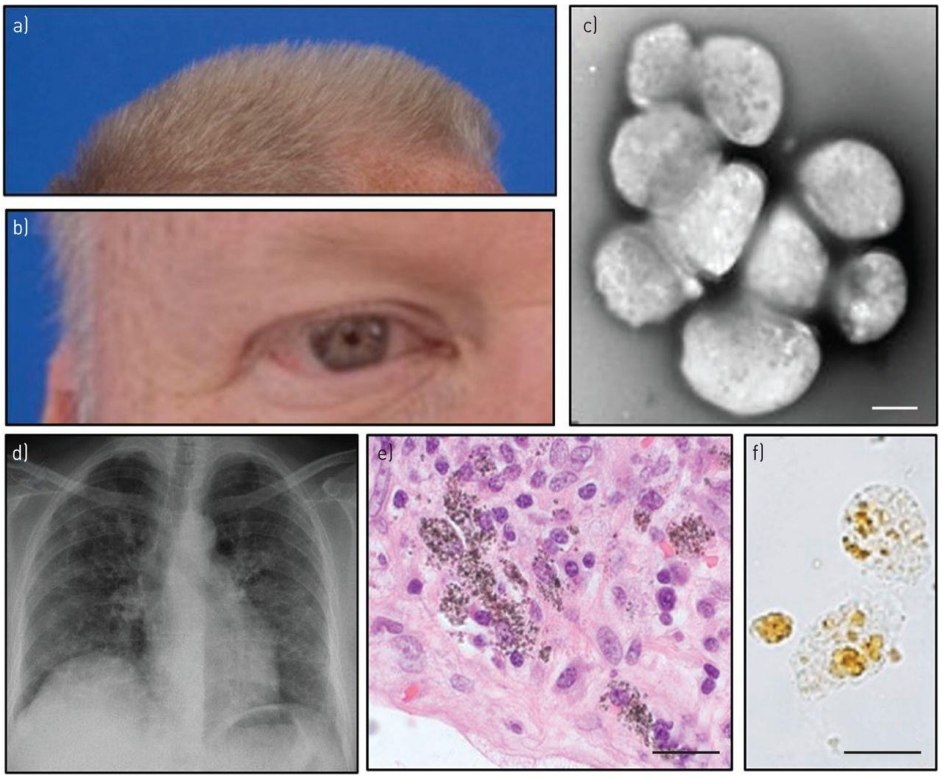

Fig 5.34: Hermansky Pudlak Syndrome 2 (HPS2), Adapted from [236, 237, 238, 239]. The figure shows the hair, skin, iris, lung deformations of Hermansky Pudlak syndrome 2 patients.

5.43. Disease 43

Disease name: Fructosuria, Essential (FRUCT)

- Gene name: KHK
- Protein name: Ketohexokinase
- Inheritance: Autosomal Recessive

This is an Autosomal Recessive disorder. Can be onset at any age. This is a rare type of disease. This disease causes because of Deficiency of Fructokinaseenzyme activity. Some features are: Fructosemia and presence of Fructosuria following ingestion of fructose and related sugar. This disease is Asymptomatic or Harmless by clinically. This disease is also known as Ketohexokinase deficiency. Heterozygous mutation on KHK gene at 2p23 is associated with this disorder. Liver tissue is the affected tissue [162, 163, Malacard].

5.44. Disease 44

Disease name: Fanconi Anemia, Complementation Group T (FANCT)

- Gene name: UBE2T
- Protein name: Ubiquitin Conjugating Enzyme E2 T
- Inhertitance: Autosomal Recessive

This is an Autosomal Recessive disorder. This disorder affacts all the bone marrow element and forms Anemia. Anemia, Leukopenia and Thrombopenia, associated cardiac, renal and limb malformation, Dermal pigmentation changes and Predisposition to the development of Malignancies, these are some characteristics of this disorder. This disorder is also known as Fanconi Anemia complementation group T. Heterozygous mutation on UBE2T at chromosome 1q32 is responsible for this disorder [164, 165, Malacard].

5.45. Disease 45

Disease name: Short Sleep, Familial Natural, 1 (FNSS1)

- Gene name: bHLHE41
- Protein name: Basic-Helix-Loop-Helix Family Member E41
- Inheritance: Autosomal Dominant

Short Sleep Familial Natural 1 (FNSS1) is an autosomal dominant disorder. It is a type of sleep disorder. Patients have less sleep in 24 hours period comparatively the normal sleep time. This disorder is also known as Sleep Natural Familial Type 1. bHLHE41 gene mutation of Heterozygous mutation at chromosome 12p12 is associated with this disorder [166, Malacard].

5.46. Disease 46

Disease name: Hypoplastic Left Heart Syndrome (HLHS)

- Gene name: TBX20
- Protein name: T-Box Transcription Factor 20
- Inheritance: No Information

Hypoplastic Left Heart Syndrome (HLHS) is not an inherited disorder. It is a physical problem that grows from birth. The patients of this disorder cannot grow a developed Left side, Heart. This includes the aorta, aorta valve, left ventricle and mitral valve. As the blood supply get irregular, the whole body gets less Oxygen. Body organs do not get Oxygen full blood. The symptoms of this syndrome are breathing problem, pounding heart, weak pulse, ashen or bluish skin color. This disorder is also known as HLHS. TBX20 gene mutation is associated with tis disorder. Ambrisentan and Bosentan drugs are mentioned for the treatment of this disorder. Skin, Heart and Brain are the affected tissues. It is a rare disease, prevalence is only 1-5/10000 (United States, Europe, Austria, Belgium, Croatia, Denmark, France, Germany, Hungary, Ireland, Malta, Norway, Switzerland, United Kingdom, Ukraine, Sweden), 1-9/100000 (Italy, Netherlands, Poland, Portugal, Spain, China). Onsets on Antenatal, Neonatal ages [169,170].

5.47. Disease 47

Disease name: Cardiomyopathy, Dilated, 1a (CMD1A)

- Gene name: LMNA
- Protein name: Lamin A/C
- Inheritance: Autosomal Dominant

Cardiomyopathy Dilated 1a (CMD1A) is an Autosomal Dominant disorder. Onsets on adult ages. The characteristics of this disorder are Cardiac Dilation and Reduced Systolic function. Some other characteristics are Ventricular dilation and impaired systolic function. Which as a result creates Congestive heart failure and Arrhythmia. Patients have a high risk of immature death. This disease is also known as Dilated Cardiomyopathy 1a. Heart, Liver and Skeletal Muscle are the affected tissues (Fig 5.35). Heterozygous mutation of LMNA gene at 1q22 chromosome is associated with this disorder. Liver Extracts has been mentioned as the drug for the treatment [171, 172].

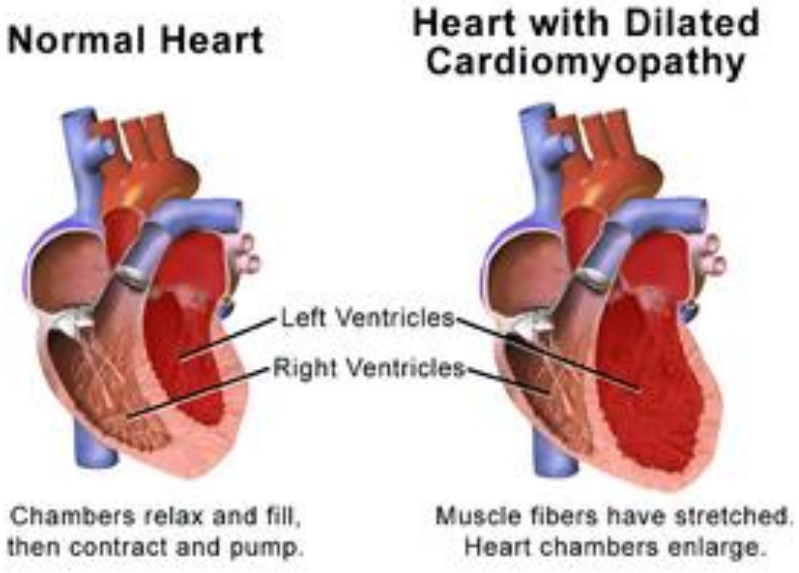

Fig 5.35: Cardiomyopathy, Dilated, 1a (CMD1A), Adapted from [240]. The figure shows the irregular pump of blood from their heart of a Cardiomyopathy Dilated 1a (CMD1A) patient.

5.48. Disease 48

Disease name: Bietti Crystalline Corneoretinal Dystrophy (BCD)

- Gene name: CYP4V2
- Protein name: Cytochrome P450 Family 4 Subfamily V Member 2
- Inheritance: Autosomal Recessive

Bietti Crystalline Corneoretinal Dystrophy (BCD) is Autosomal Recessive disorder. Symptoms start to show in the 2nd or 3rd decades of a patient's life. Characteristics of this disorder Numerous small, Yellow or White crystal-like deposits of fatty compounds accumulate in light sensitive tissues that lines the back of the eye (Fig 5.36). That is why patients start to have vision problems at their teen ages or twenties. Most of the patients get totally blind after 40 years of ages. This disorder is also known as Bietti Crystalline Dystrophy. Retina, Eye and Skin are the affected tissues. Homozygous or Compound Heterozygous mutation of CYP4V2 gene at chromosome 4q35 is associated with this disorder [173, 174, 175, 176, Malacard].

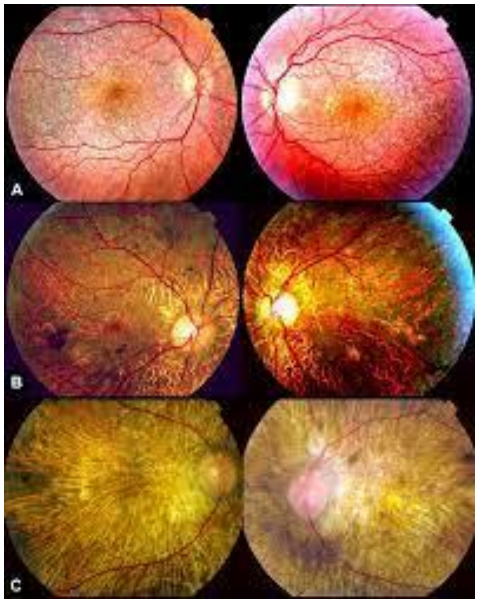

Fig 5.36: Bietti Crystalline Corneoretinal Dystrophy (BCD), Adapted from [241]. The figure shows the affected irises of Biett Crystalline Corneoretinal Dystrophy (BCD) patients.

5.49. Disease 49

Disease name: Chromosome 1p36 Deletion Syndrome

- Gene name: SPEN
- Protein name: Spen Family Transcriptional Repressor
- Inheritance: Multigenetic disorder

Chromosome 1p36 Deletion Syndrome is a Multigenetic disorder. Rare neurological type disorder, prevalence is only 1-5/10000 (United States). Onsets on Antenatal, Neonatal ages. At any age patients can die. Developmental anomalies during embryogenesis. This disorder is finally causing severe Intellectual disabilities (Fig 5.37). Affected patients mostly cannot speak or can speak only few words. A deletion of genetic material from a specific region of chromosome 1 causes this disorder. Mostly this disease is not inherited. About 20% of patients of this disorder inherit the chromosome with a deleted segment from an unaffected parent. This disease is also known as 1p36 deletion syndrome. SPEN (Spen Family Transcriptional Repressor) gene is associated with disorder. Affiliated tissues include heart, kidney and eye [177,178,179 Malacard].

Fig 5.37: Chromosome 1p36 Deletion Syndrome, Adapted from [242]. The figure showing Chromosome 1p36 deletion syndrome affected patients whose having hearing loss, heart defects, facial deformations, renal abnormalities, brain abnormalities.

5.50. Disease 50

Disease name: Fibrodysplasia Ossificans Progressive (FOP)

- Gene name: ACVR1
- Protein name: Activin A Receptor Type 1
- Inheritance: Autosomal Dominant

Fibrodysplasia Ossificans Progressive (FOP) is an Autosomal Dominant disorder. Onsets on childhood, death can happen at any ages. Very rare disease, prevalence is only <1/1000000 (Worldwide, United Kingdom, Spain, Spain, Europe) 1-9/1000000 (France). 1 in 1,600,000 new born of worldwide are recorded of having FOP disorder. About 800 people are recorded as a patient of FOP worldwide. Onsets on childhood and death can happen at any age. Characteristics are: Skeletal muscle and Connective tissues are

gradually replaced by bone (Fig 5.38). Such as: Tendons and Ligaments, these tissues turn into bone after being affected. Patients born with abnormal huge toes. This disorder is also known as Myositis Ossificans Progressive. Heterozygous mutation on ACVR1 gene at chromosome 2q24 is associated with this disorder. Isotretinoin and Tin Fluorides drugs have mentioned for the treatment of this disease. Bone, Skeletal muscle and Skins are the affected tissues [180,181,182,183, Malacard].

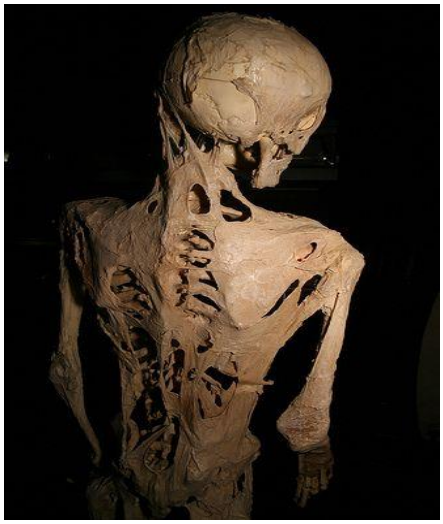

Fig 5.38: Fibrodysplasia Ossificans Progressiva (FOP), Adapted from [243]. The figure shows the muscles of a FOP patient which eventually turned into bones by growing ages.

5.51. Disease 51

Disease name: Myasthenic Syndrome, Congenital, 12 (CMS12)

- Gene name: GEPT1
- Protein name: Glutamine Fructose-6-Phosphate Transaminase 1
- Inheritance: Autosomal Recessive

Myasthenic Syndrome Congenital 12 (CMS12) is an Autosomal Recessive disease. This disease onsets on the first decade of the patient's life, favorable response to acetylcholinesterase inhibitors, distinct disorder from acquired limb-girdle myasthenia and congenital limb-girdle myasthenia. It is known as Congenital Myasthenic syndrome. Characteristic of this disorder are: Failure of Neuromuscular transmission including pre-synaptic, synaptic and post synaptic disorder. These are not auto-immune origin. This

disorder is also known as Congenital Myasthenic syndrome 12. Homozygous or Compound Heterozygous mutation of GEPT1 gene at chromosome 2p13 is associated with this disorder [184, 185, Malacard].

5.52. Disease 52

Disease name: Oligodendroglioma

- Gene name: IDH2
- Protein name: Isocitrate Dehydrogenase (NADP (+) 2)
- Inheritance: Multigenic / Multifactorial disorder

Oligodendroglioma multigenic or multifactorial inherited disorder. Prevalence 1-9/1000000 (Europe). Onsets any ages of life. Oligodendrogliomas are brain tumors arising from oligodendrocytes. Some symptoms are: Seizures, Headache and changes in personality (Fig 5.39). The exact cause of Oligodendrogliomas is unknown. Chromosome abnormalities are shown in chromosome 1p and 19q. Surgical removal of the tumor by radiation therapy or Chemotherapy. The disorder is also known as Oligodendroglial Neoplasm. IDH2 gene mutation is associated with this disorder. Lomustine and Vincristine drugs have been mentioned for the treatment. Bone, Brain and Eye are the affected tissues [186, 187, Malacard].

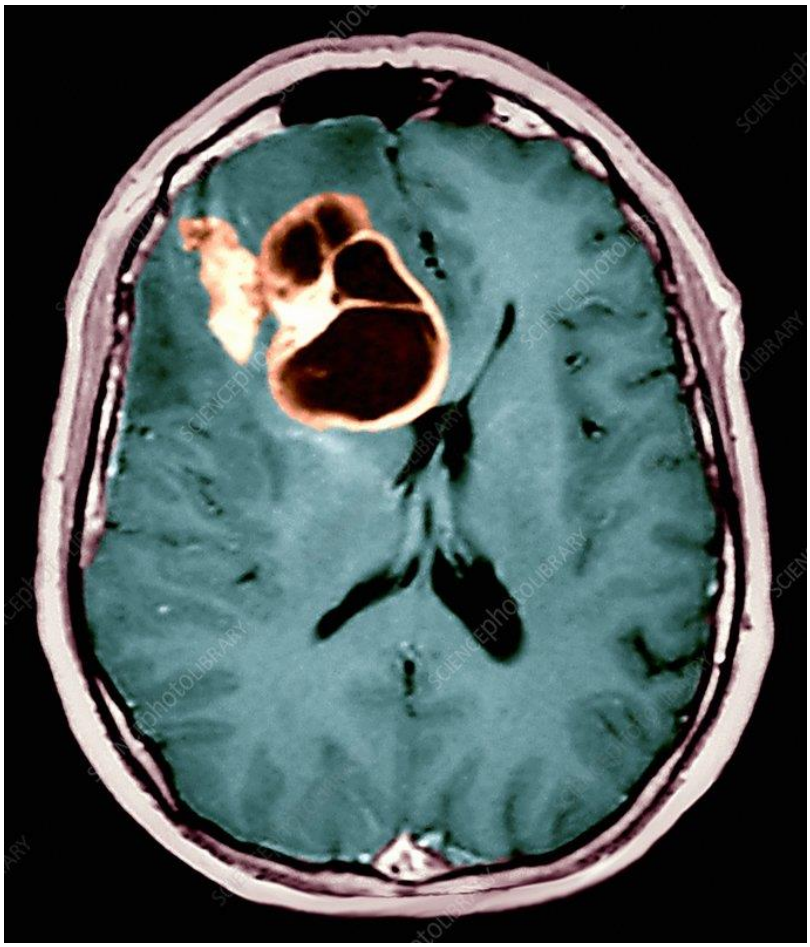

Fig 5.39: Oligodendroglioma, Adapted from [244]. The figure shows the development of tumor in the brain and gradually turns into brain cancer.

5.53. Disease 53

Disease name: Spastic Paraplegia 24, Autosomal Recessive (SPG24)

- Gene name: SPG24
- Protein name: Spastic Paraplegia 24
- Inheritance: Autosomal Recessive

Spastic Paraplegia 24 (SPG24) is an Autosomal Recessive disease. A rare type of disease that the prevalence is only <1/1000000 (Worldwide). Prevalence of this disorder is only <1/1000000 (Worldwide), so this is a rare disorder. Onsets on Infancy ages. This rare pure form spastic paraplegia disease is characterized with an onset in infancy of lower limb spasticity associated with gait disturbances, Scissor gait, Tiptoe walking, Clonus and

increased deep tendon reflexes. This syndrome is also known as SPG24. Mutation on SPG24 on chromosome 13q14 is associated with this disorder [188, 189, 190, Malacard].

5.54. Disease 54

Disease name: Mucoepithelial Dysplasia Hereditary (HMD)

- Gene name: SREBF1
- Protein name: Sterol Regulatory Element Binding Transcription Factor 1
- Inheritance: Autosomal Dominant

Mucoepithelial Dysplasia Hereditary (HMD) an Autosomal Dominant disorder. Chronic mucosal lesions associated keratitis, Non-scarring Alopecia, Keratosis pilaris and Perineal Intertrigo are the characteristics of the disorder. Most common symptoms are: excessive hair loss, patchy red skin and round perineum and red gums. Based on the symptoms, the diagnosis of HMD is provided. This disorder is also known as Mucoepithelial Dysplasia. Skin, Eye and Tongue are the affected tissues (Fig 5.40). Heterozygous mutation of gene SREBF1 at chromosome 17p11 is associated with this disorder [191, 192, 193, 194, Malacard].

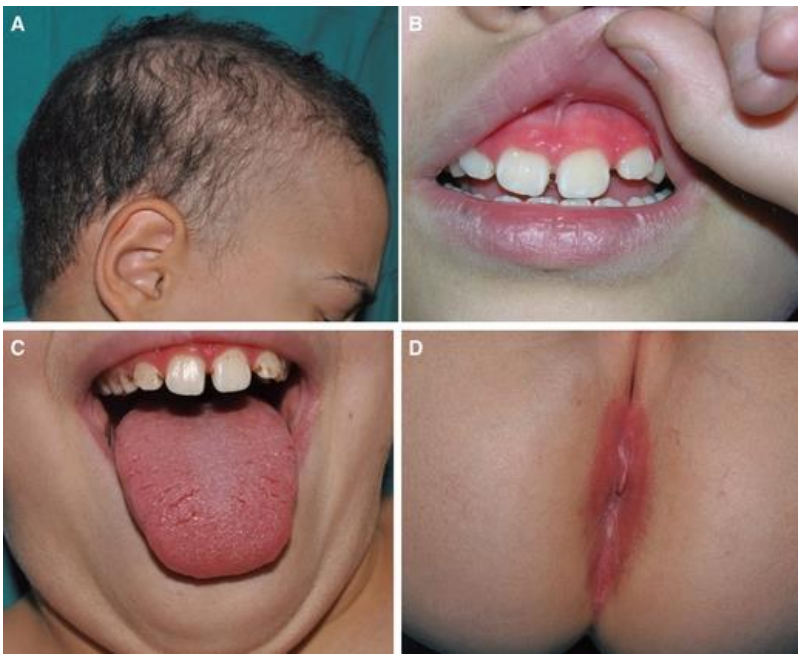

Fig 5.40: Mucoepithelial Dysplasia, Hereditary (HMD), Adapted from [245]. The figure shows the reddish spots of an HMD patient.

5.55. Disease 55

Disease name: Elsahy-Waters Syndrome (ESWS)

- Gene name: CDH11
- Protein name: Cadherin 11
- Inheritance: Autosomal Dominant

Elsahy Waters Syndrome (ESWS) is an Autosomal Dominant disorder. A rare type disorder, prevalence is only <1/1000000 (Worldwide). Onsets on Neonatal stage. Brachycephaly, Facial Asymmetry, Marked Hypertelorism, Proptosis, Blepharochalasis Midface Hypoplasia, Broad nose, Radicular dentin dysplasia with consequent obliterated pulp chambers, apical translucent cysts etc. (Fig 5.41) These are the characteristic of this disease. Also known as brachioskeletogenital syndrome. Skin and Spinal cord are the affected tissues. Homozygous mutation on CDH11 gene at chromosome 16q21 is associate with this disorder [195, 196, 197, 198, Malacard].

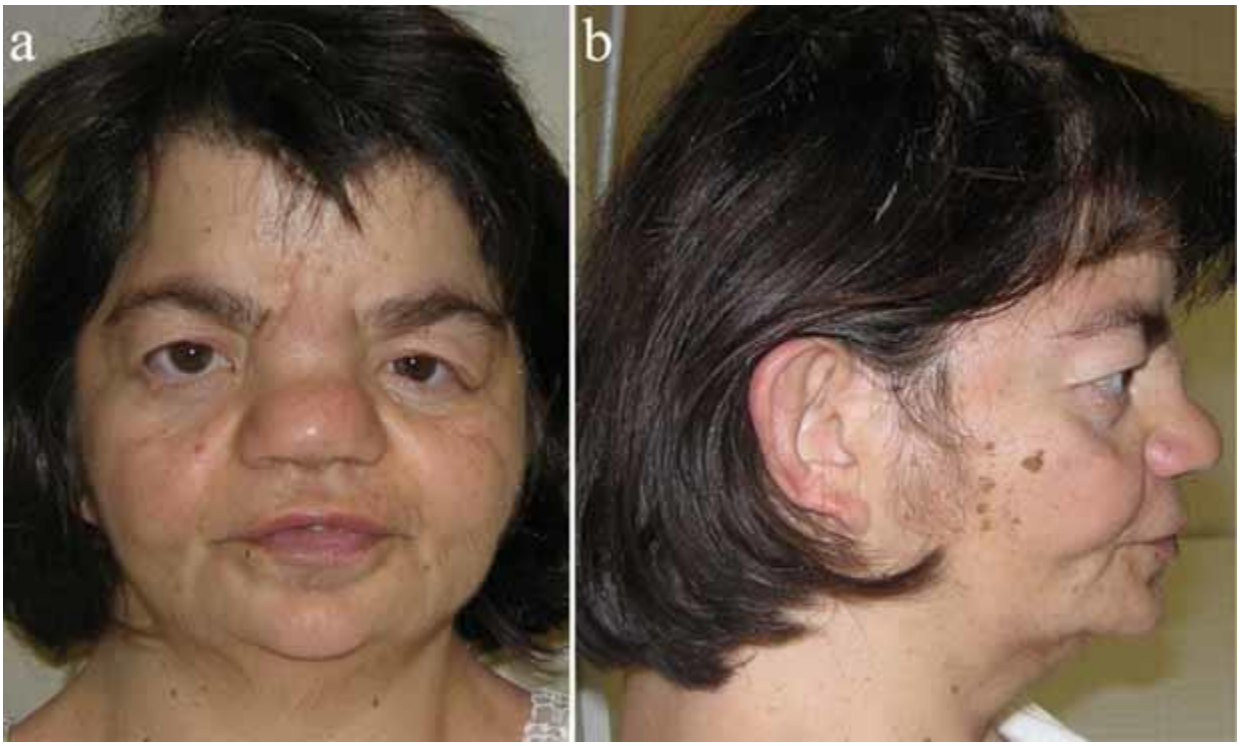

Fig 5.41: Elsahy-Waters Syndrome (ESWS), Adapted from [246]. The figure shows a Elashy Waters syndrome patient having facial deformations.

5.56. Disease 56

Disease name: Renal Dysplasia

- Gene name: GATA3
- Protein name: GATA Binding Protein 3
- Inheritance: Autosomal Dominant

Renal Dysplasia is an Autosomal Dominant Disorder. Prevalence is only 1-5/10000 (Europe). Onsets on any age. Death can also happen at any age. A rare type of Renal malformation disorder. In this disorder kidneys development are abnormal which leads to malformation of the actual shape of Kidney (Fig 5.42). Embryological tissues such as Mesenchymal collarettes or other forms of undifferentiated and metaplastic tissues form in the kidneys. This disorder can be Unilateral or Bilateral segmental and severity varies patients to patients. GATA3 gene mutation is associated with this disorder. Pharmaceutical solutions and Ibuprofen drugs are mentioned for the treatment. Kidney, Testis and Uterus are the affected tissues of this disorder [Malacard].

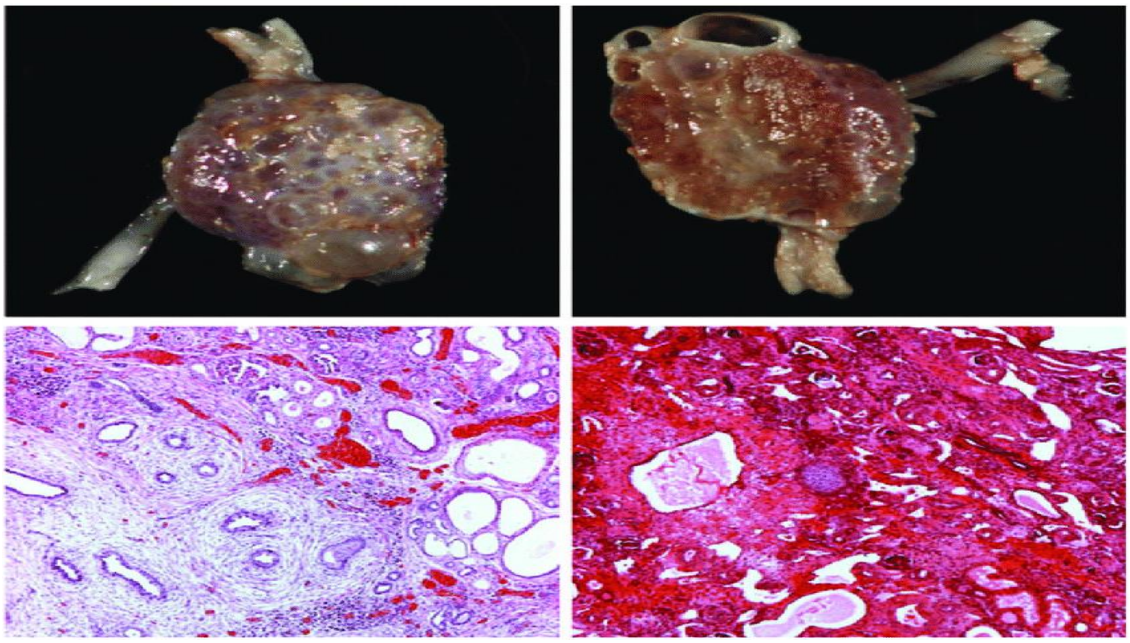

Fig 5.42: Renal Dysplasia, Adapted from [247]. The figure shows the disturbances of kidney cells.

5.57. Disease 57

Disease name: Cowden Syndrome (CD)

- Gene name: PTEN
- Protein name: Phosphate and Tensin Homolog
- Inheritance: Autosomal Dominant

Cowden syndrome (CD) is an Autosomal Dominant disorder. Prevalence is only 1-9/1000000 (Netherlands, Europe). This disorder is characterized by Multiple Noncancerous tumors like growth, which is called Hematomas (Fig 5.43). There is a risk of developing certain cancers. CD patients usually have large head. This disorder is also known as Cowden disease. Thyroid and Breast skin are the affected tissues. Everolimus and Miconazole drugs are mentioned as the treatment of this disease. PTEN gene mutation is associated with this disorder [199, 200, Malacard].

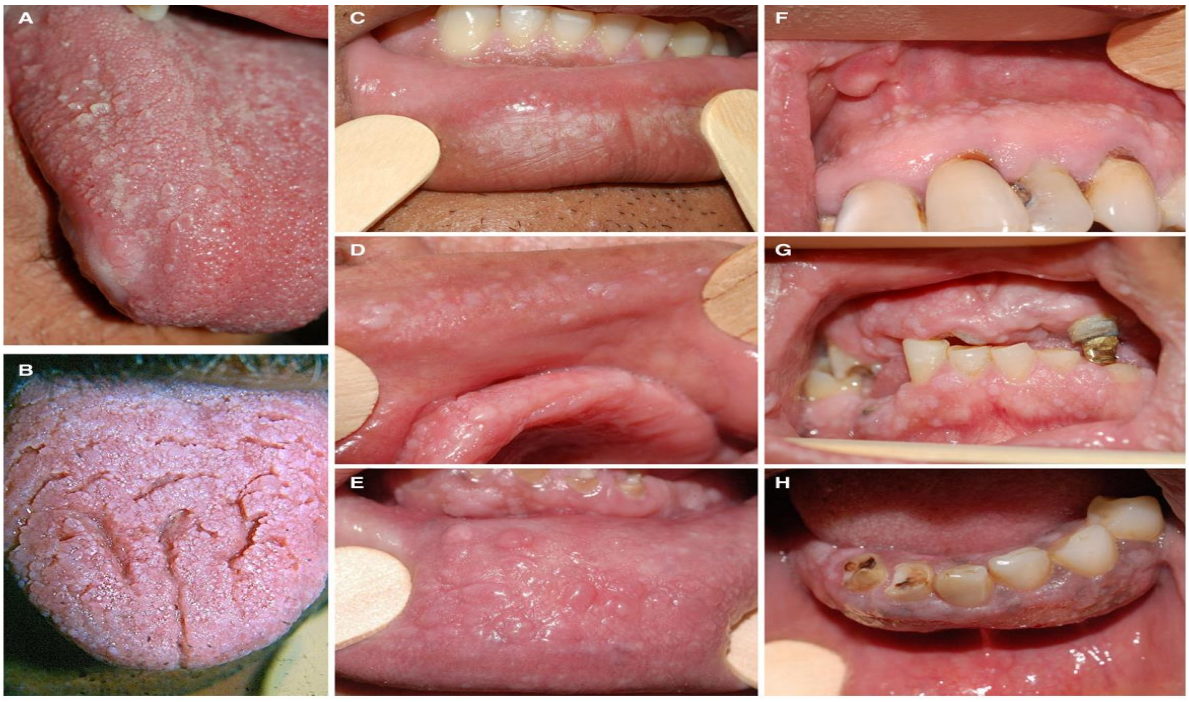

Fig 5.43: Cowden Syndrome (CD), Adapted from [248]. The figure shows the skin diseases of a Cowden syndrome patient on his mouth, tongue and lips.

6. Conclusion

bHLH proteins are one of the most essential proteins of the transcription process. In this review paper, some statistics about the symptoms, affected tissues, chromosomes, mutations and locations of the diseases have been highlighted. In the affected tissue chart Nervous system related tissues show the highest results. That means, in these diseases, most of the diseases affect nervous system related tissues. Then gradually comes Musculoskeletal system, Circulatory system and Skin and External systems, which are same in ranges. Next is Sensory organs, then Internal organs, then is Reproductive organ and lastly the least affected tissues are from Hormonal glands and then some other organs are also included.

In the Inheritance chart, Autosomal Dominant takes the highest place which means most of the diseases are Autosomal Dominant in inheritance. In 2nd highest position there is Autosomal recessive. The gradually come No information sections, Somatic mutations, Multigene/Multifactorial mutations and lastly, X-linked recessive mutations.

In the Mutation chart, Heterozygous mutation takes the highest places which is 43%, next is Homozygous mutation which is 34%, then comes No information 15%, next is Somatic mutation which is 3% and lastly comes Germline mutation which is only 2%.

In the chromosome chart, the percentages of different mutated and disease related chromosomes are shown. The chart says that, the 7th chromosome is the most mutated and disease created chromosome and 13th, 14th, 16th and 21st chromosomes are the least mutated and disease created chromosomes.

The symptoms bar says that because of the attack of the diseases some symptoms are seen in patient's body. The highest showing symptoms of the disorders that are responsible for genetic mutation comes from Skin and External system of human body, 2nd highest symptoms come from Sensory system, then comes Nervous system, then Skeletal system, then Cardiac system, then next comes Circulatory system, then Renal system, Muscular system, Reproductive system, Respiratory system, Endocrine system, Cancer and others. Scientists are still working on these disorders. Some drugs have already been invented

against these disorders; most diseases have no drugs. It has been expected that very soon scientists will be able to find more drugs or treatments against these genetic disorders.

bHLH transcription factor belongs from the super transcription factors family. It is widely distributed in Eukaryotes like Human. bHLH proteins are mainly involved in developmental process. During transcription process of any organisms like human, bHLH protein plays a vital role of developmental process of organs. During the process a simple mutation can create disturbance the process and form deformities of the organs. That means, mutations on bHLH proteins can develop a physically or developmentally disabled human being with birth defects.

In this review, we have seen that Split-hand/foot malformation with long bone deficiency 3 (SHFLD3), Camptosynpolydactyly, Complex (CCSPD), Syndactyly, Mesoaxial Synostotic, with Phalangeal Reduction (MSSD), Feingold Syndrome 1 (FGLDS1), Williams-Beuren Syndrome (WBS), Ablepharon-Macrostomia Syndrome (AMS), Craniosynostosis 1 and many more disorders are developmental disorders. Most of the mutated related disorders are developmental disorders as the main role pf bHLH protein is developing perfect organs.

Some diseases are involved in vision related or eye related disorders. Retinitis Pigmentosa 85 (RP85), Coloboma, Osteopetrosis, Microphthalmia, Macrocephaly, Albinism and Deafness (COMMAD), Persistent hyperplastic primary vitreous, autosomal recessive (PHPVAR) etc are eye or vision related disorders.

Some disorders are reproductive organ related disorders like, Prostate cancer, Spermatogenic Failure 32 (SPGF32), Ovarian Dysgenesis 5 (ODG5), Premature ovarian failure 6 (POF6) these are some reproductive organ deformities related disorders. Some sleep related disorders are also seen like, Short Sleep Familial Natural 1 (FNSS1),

Delayed Sleep Phase Disorder (DSPD) these are some sleep related disorders. bHLH protein mutation syndromes can make people physically as well as mentally disabled. Some of them are life threatening like, Cardiomyopathy, Dilated, 1a (CMD1A) is highly life threatening.

However, scientists could not find the treatments of all these disorders. Some drugs are provided from some primary treatment but most of the disorders are not curable. As these are mostly developmental disorders, the treatment would not be easy. These are genetic disorders and people get these syndromes from the very beginning of their lives. Hopefully understanding the multiple diseases connected by bHLH gene mutations will allow scientists to find the treatment for the kids affected with such mutations of bHLH.

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