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Juvenile Batten Disease – Past and Present Diagnosis

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Editorial

Juvenile Batten disease or Juvenile neuronal ceroid lipofuscinosis (JNCLs) inherit in autosomal recessive pattern leading to neurodegenerative disorder of onset in children between 4 to 8 years. The symptoms associated with this disease include cognitive decline, seizures, movement disorder, progressive dementia, epilepsy and retinopathy which was first described in 1903. This disease has estimated incidence range from 7/100,000 births worldwide [1] and caused by genetic mutations which lead lipofuscins to accumulate within the tissues of human body [2]. In NCLs, nearly 400 pathogenic mutations have been reported and they are included in NCL Mutation Database [3]. Till date, there is no established treatment available which can prevent or stop the disease pathogenesis. Nearly fourteen genes have been reported to be found associated with various types of neuronal ceroid lipofuscinosis and these genes (Figure 1) harbor majority of mutations leading to development of batten disease phenotypes [4]. The lists of identified genes that cause NCLs are explained [5] in Table 1.

The ceroid-lipofuscinosis-3 (CLN-3) gene located in chromosome 16 at position p.12.1 Containing 17 exons with protein coding 438 amino acids with 5-7 transmembrane domains. This gene is coded by a CLN3 or Battenin protein which is found in the cell membranes such as lysosomes and endosomes and CLN3 mutations are considered as the important risk factors for Juvenile NCL [6]. There are several diagnosis methods available such as Biochemical profile of blood, screening of candidate gene (CLN), clinical phenotype, electroencephalogram, examination by radiological methods, and level of functional impairment. However, all the diagnosis methods can be performed during the initial stage of NCLs, previous reports infers the usage of candidate gene screening for routine use [7]. Prenatal diagnosis is performed for Batten disease in the families where mutations in CLN3 gene are already known.

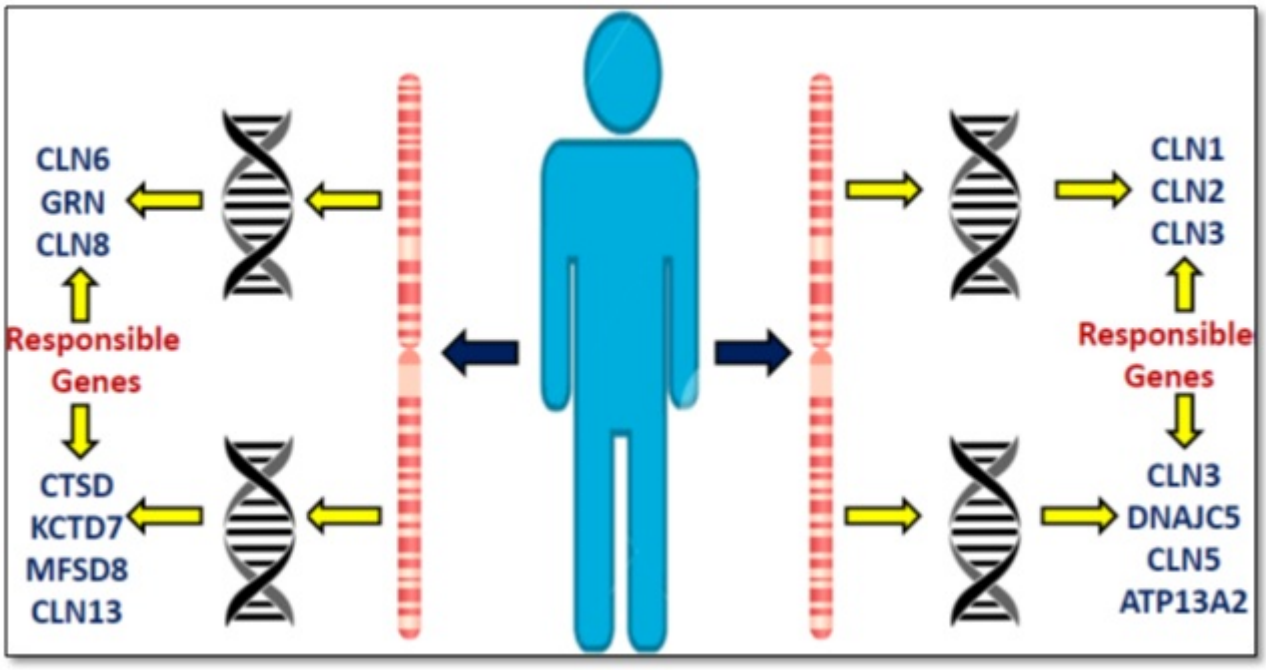

Figure 1: The candidate genes that cause neuronal ceroid lipofuscinosis.

In 1995, The International Batten Disease Consortium has documented 1.02 kb deletion (7th and 8th exon) in CLN3 gene which is responsible for 73% of NCLs. This mutation causes truncated protein leading to premature stop codon resulting in clinical phenotype [8]. The same deletion (mutation) was identified in 139/188 (74%) patients affected with NCLs of different ethnic populations in the year 1997 [9]. A study comprising 11 patients from Australia of different age group affected by neuronal ceroid lipofuscinoses showed mutations such as c.

560T>C, c.184C>T, c.662A>G, c.200T>C, c.308G>A c.712T>A, c. 713T>C in CLN6 gene and all had functional effects [10]. A study conducted in Denmark from 1971 to 2003 in the 35 patients (19 males, 16 females) of JNCLs identified various clinical features such as cataract, glaucoma and they were also the carriers of 1.02 kb deletion in the CLN3 gene [11]. Whole-exome sequencing was performed to identify the variations in late-infantile NCLs in 3 siblings, which revealed novel mutations in MFSD8 gene such as c.1361T.C (p.Met454Thr) and c.1219T.C (p.Trp407Arg) with their clinical phenotypes [3].

S. No	Genes	Chromosomal location	Total Exons	Protein (Amino acids)
1	Ceroid lipo fuscinosis, neuronal-1 (CLN1/PPT1)	1p34.2	9	306
2	Tripeptidyl Peptidase 1 (CLN2/TPP1)	11p15.4	13	563
3	Ceroid-Lipofuscinosis, Neuronal 3 (CLN3)	16p12.1	17	438
4	DnaJ Heat Shock Protein Family (Hsp40) Member C5 (CLN4/DNAJC5)	20q13.33	5	198
5	Ceroid-Lipofuscinosis, Neuronal 5 (CLN5)	13q22.3	4	407
6	Ceroid-Lipofuscinosis, Neuronal 6, Late Infantile, Variant (CLN6)	15q23	11	311
7	Major Facilitator Superfamily Domain Containing 8 (CLN7/MFSD8)	4q28.2	13	518
8	Ceroid-Lipofuscinosis, Neuronal 8 (CLN8)	8p23.3	3	286
9	Cathepsin D (CLN10/CTSD)	11p15.5	9	412
10	Granulin (CLN11/GRN)	17q21.31	13	593
11	ATPase 13A2 (CLN12/ATP13A2)	1p36.13	29	1175
12	Cathepsin F (CLN13/CTSF)	11q13.2	13	484
13	Potassium Channel Tetramerization Domain 7 (CLN14/KCTD7)	7q11.21	4	289

Table 1: Summary of the identified genes that cause neuronal ceroid lipofuscinosis.

There are several gene panels available for diagnosis of several diseases such as xGen Pan-Cancer Panel, TruSeq Amplicon-Cancer, OncoGxOne-Discovery Cancer and Gyne Carta Panel. By considering the previously published studies which document the known mutations, 14 candidate genes (CLN) can be incorporated into a genetic panel for prenatal screening in juvenile batten disease; finally it helps us to reduce the disease burden as preventive measures. Pre-natal genetic testing identifies whether an individual carries a copy of NCLs-causing mutations. Likewise, predictive genetic testing to establish whether a healthy child will convert to Batten disease and the parents of affected individuals may screen their other children are carriers of the gene mutations. Due to improvement of robust technologies in the recent years, the diagnosis of genetic disorders has become easy, fast and more precise. High throughput molecular testing contributes as an indispensable technique for establishing accurate diagnosis and to facilitate the genetic counselling.

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