Biological basis of dyslexia: A maturing perspective

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Dyslexia is a common childhood learning disability. The occurrence of dyslexia ranges from 3 to 17.5%. Etiology remains largely unknown, but substantial evidence from multidisciplinary research suggests that dyslexia is a disorder of genetic origin with a basis in the brain. Many genetic studies indicated that different loci are involved in genetic predisposition of dyslexia. The loci on 6p21.3, 15q15–21 and 18p11.2 have been identified as promising candidate gene regions. Since it is a complex disorder, identification of the specific genetic variants may bring a comprehensive explanation for the etiology of dyslexia. This review provides recent understanding in the field of neurobiology of dyslexia.

Keywords: Brain, candidate gene, chromosomes, dyslexia, linkage, loci.

LANGUAGE is truly a unique human gift, a complex process that enables communication and social functioning. Language gave human an enormous edge over other animals and increased the chances of humans survival[1]. Most children acquire language naturally in the sequence of listening, speaking, reading and writing. Failure in any of these processes may lead to lifelong socioeconomic and mental health consequences[2]. There are many causes of language disability; the most common is dyslexia. No single definition currently exists to adequately define dyslexia and there is much controversy regarding the definition of dyslexia due to the complex expression of the disorder. But most of the definitions do agree that it cannot be attributed to any impairment in vision or hearing or intelligence and it is widely accepted that cognitive skills which are related to reading are affected. One of the most acceptable definitions is that it is a difficulty in learning to read and spell despite adequate education, intelligence and socio-cultural opportunities and without any obvious sensory deficits[3]. Dyslexia accounts for 80% of learning disabilities. Prevalence of the trait ranges from 3 to 17.5% of school-age children[4–6]. It is found that males are more frequently affected than females[7]. Hormonal factors such as foetal testosterone levels during late pregnancy may play a critical role and this is possibly reflected in the large male predominance of dyslexia[8].

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Symptoms

Acquisition of reading-related skills requires the coordination of many areas in the brain involved in visual, motor and cognitive activities. Thus dyslexia can result from defects in any of the above processes[9]. Specific reading problems in dyslexia include difficulties in single-word decoding, processing new words, making distinction between similarities and differences; also dyslexics show reversal and transposition of words and letters[10]. Dyslexics are usually clumsy with poor motor balance and coordination, and they show delayed early milestones such as crawling, walking and speech development. Dyslexic children differ significantly from reading-age controls in tasks involving automation of motor skill, motor reaction times, speed naming, time estimation, attention and visuospatial skills. They also have difficulties in map-reading, confusion with left and right, and fail to become right or left-handed. Dyslexia has a complex link with immune diseases and sex hormones[11–14].

Etiology

Evidences for origin of dyslexia have been increasingly accumulating during the last two decades. Although multiple etiologies are proposed for this complex trait, the exact cause still remains unknown; but substantial evidence from genetic and neurological studies suggests that dyslexia is a disorder which is influenced by genetic factors and the underlying deficit is in the language areas of the brain. Many theories are put forward to explain the etiology of dyslexia. The main theories are discussed below.

Phonological theory of dyslexia

Brain recognizes language in a hierarchical order. The upper levels deal with semantics (the meaning of words), syntax (grammatical structure) and discourse (connected sentences). The lower levels of hierarchy deal with breaking sounds into separate small units called phonemes. Thus before words can be comprehended at higher levels in the hierarchy, it has to be decomposed into phonologic constituents that the alphabetic characters represent. To achieve this, the reader should have conscious awareness of the phonological structure of spoken words. If the reader lacks this

awareness, he/she will have difficulty in learning the relationship between letters and sounds, as well as applying those letter/sound correspondences to sound out unknown words[6]. Individuals with dyslexia have difficulties with phonological decoding of orthographic symbols, and this is the significant source of reading problems[15]. Since most dyslexics show deficits in phoneme processing, it was suggested that phonological deficit is the most significant and consistent marker of dyslexia[16]. Brain imaging studies in dyslexics in response to a phonological task indicate under-activation of posterior brain regions (Wernickes's area, angular gyrus, extrastriate and striate cortex) and relative over-activation in anterior regions (inferior frontal gyrus, BA46/47/11). These brain activation patterns provide evidence of an imperfectly functioning brain system for segmenting words into their phonologic constituents[6,17]. However, this theory does not account for symptoms such as impairment in visual perception and problems with motor coordination that are found in dyslexics.

Cerebellar theory of dyslexia

This theory postulates that the cerebellum of dyslexics is slightly dysfunctional[18]. Evidence for this theory comes from poor dyslexic performance in coordination, balance and time estimation[19]. The normal pattern of cerebellar asymmetry is anomalous in dyslexia. The ratio of left grey matter to right grey matter was greater in the cerebella of those with dyslexia than in the controls. Those with more symmetric cerebella made more errors on a nonsense word reading measure of phonological decoding deficit[20]. The right cerebellum has also shown to display a functional deficit in dyslexics, exhibiting decreased blood flow in response to both learned and novel motor tasks[21]. Cerebellar laterality is ipsilateral to handedness, and right-handed people have a larger proportion of right cerebellar grey matter. This association is also anomalous in dyslexic individuals. Biochemical ratios (choline/noradrenalin and creatine/noradrenalin) in the right cerebellum were significantly altered in dyslexics[22]. There are evidences of reduced cerebellar activity in dyslexics performing a motor learning task. There are indirect evidences of cerebellar dysfunction in dyslexics which include delayed motor milestones such as crawling, walking and a characteristic clumsiness[14,23,24]. All these evidences suggest that there are morphological and metabolic alterations in the cerebellum of dyslexics which relate to reading skills, motor skills and handedness.

Magnocellular theory of dyslexia

The magnocellular theory has recently gained much attention among dyslexia researchers. Neurons in the magnocellular layers of the lateral geniculate nucleus are sensitive to motion perception and temporal resolution, and are important for the control of eye movements[25]. The magnocellular pathway along with the parvocellular pathway connects the retina to the occipital and parietal lobes of the brain and information brought in by the eye is processed here. Impaired function of magnocellular pathway will lead to destabilization of binocular fixation, which leads to visual confusion and letters then appear to move around. It has been found that binocular control of dyslexics is poor. Their eyes are unsteady when they are attempting to view small letters: hence their vision is unstable and they tend to make visual reading errors[26]. Psychophysical and anatomical studies provide increasing evidence that 75% of dyslexics exhibit visual processing abnormalities that may confine to particular portions of the visual system[27]. Postmortem studies of dyslexic individuals have shown that magnocells (large neurons) of the lateral geniculate nucleus were disordered and 20% smaller than that of controls[28,29]. Dyslexics failed to produce functional activation in V5/MT area (which is part of the magnocellular system) in response to moving stimuli. Magnocellular dysfunction is not restricted to the visual pathways but also in other sensory modalities, auditory, tactile, motor and phonological abilities[25]. This is evident from poor performance of dyslexics in tactile domain and co-occurrence of visual and auditory problems in some dyslexics[30,31]. These studies suggest that many of the dyslexics have impairment in the visual system and it may be another marker of the disorder.

Subtle brain anomalies associated with dyslexia

Neuroimaging and neuro-functional studies have shed light on anatomical and functional brain differences in dyslexia. Post-mortem analysis of dyslexic brains revealed that dyslexics have microscopic cortical malformations in the language areas, particularly in both inferior frontal gyrus and temporoparietal areas of the brain in the form of ectopias (misplaced collection of neurons), microgyrias and dysplasia (loss of characteristic architectural organization of the cortical neuron)[32,33]. These microscopic observations suggest abnormal cortical maturation in dyslexic brain. In normal brain, high percentage of asymmetry is seen in the planum temporale which is involved in language processing, analysing sounds, naming objects and recalling words. MRI and post-mortem studies of dyslexic brain indicate the absence of asymmetry of the planum temporale, i.e. it is symmetrical or larger in right hemisphere[32,34]. Usually it is larger in the left hemisphere and the symmetry was due to the enlarged right hemisphere rather than the decreased size on the left[35,36]. Functional abnormalities also have been found in the planum temporale. Dyslexics who had symmetrical planum temporale performed poorly on nonword reading task. The parietal area situated in the front of the planum temporale is also less asymmetrical in dyslexics and this condition is correlated with poor phono-

logical performance[37]. Inferior frontal gyrus has a role in speech perception, rapid auditory processing and phonological aspects of reading. It is also found that reversed direction of asymmetry in the inferior frontal regions for example, dyslexics show symmetrical pattern of Brocas area 44 and 45, which has been correlated with non-word reading performance[38]. It is also found that there is a relation between extra sulci in the inferior posterior frontal gyrus and family history of developmental language disorders[39]. It has been suggested that interhemispheric transfer of sensory or motor information is impaired in dyslexics and evidence comes from differences in the callosal measurements in dyslexics[40]. Disruptions in white matter connectivity between posterior and frontal regions have also been found in dyslexic brain[41]. These anatomical and functional characteristics of the dyslexic brain are considered to be good evidence of maturational deviance which results in the origin of the reading difficulties of dyslexics. However, neurological problems that dyslexics face are mild and these differences are not universal. Till date no diagnostic conclusions have been drawn in the assessment of neurological basis of dyslexia.

Genetics of dyslexia

Genetic theory began when researchers observed that dyslexia runs in families, as familiality is the necessary condition for genetic disorders. In 1950, Hallgren[42] reported that more than 80% of the children with dyslexia had other family members with the disability. Family and twin studies indicate that genetic factors have a significant role in predisposition of dyslexia. It is found that in monozygotic twins different measures of dyslexia (phonological awareness and phonological coding) are highly heritable (50–70%) than dizygotic twins[43–45].

Studies have been reported on the inheritance pattern of dyslexia. Hallgren[42], in a study of 112 families with dyslexia, found that in 90 of them the data best fitted with an autosomal dominant transmission. Segregation analyses of dyslexia involving a total of 204 families with 1698 individuals revealed both sex-influenced autosomal transmission as well as autosomal dominant inheritance[46]. However, our preliminary studies on 28 dyslexic families suggest that 18 of them are consistent with autosomal dominant mode of inheritance, six have shown autosomal recessive pattern and in four families, the transmission is complex (unpublished data). These studies suggest that dyslexia does not always segregate in families in a simple Mendelian fashion and the mode of inheritance is complex[47–49]. The risk of dyslexia is more in relatives of dyslexics compared to the general population[50]. Siblings in families with two affected parents are more severely impaired than those in families with one affected parent[51].

As reading is a complex task, this disability could arise from deficiencies in one or more associated cognitive processes[52]. Due to this complex nature, identification of dyslexia genes is difficult task and it is most likely to be influenced by the interaction of many genetic and environmental factors[53]. With the advancement of human genome research, more efficient markers and new sampling methods of modern statistical analysis, geneticists have made substantial progress in identifying different loci, on chromosome 1, 2, 3, 6, 7, 15 and 18 (Table 1) segregating with dyslexia. These genomic regions may contain many candidate genes for dyslexia and identification of specific genetic variants is underway. Following are some of the important linkage studies on dyslexia.

Chromosome 1

Linkage analysis of nine families with polymorphic protein marker, Rh and DNA markers maps to 1p34–p36 region for dyslexia. This study reports that dyslexia is inherited in autosomal dominant fashion with high degree of penetrance[54]. Another study using parametric and non-parametric linkage (NPL) analyses supports a locus on 1p with highest NPL score[55] of 5.0.

Chromosome 2

Genome wide scan in Norwegian dyslexic family members suggests a locus on 2p15–p16, cosegregating with dyslexia in an autosomal dominant pattern. Parametric linkage analysis showed the maximum LOD score of 4.3 at the marker D2S378. This result is supported by non-parametric analysis, which suggests the locus lies in a 4cM between markers D2S2352 and D2S1337. This susceptible locus is named as *DYX3*. It is found that the haplotypes D2S378/D2S2279/D2S2183 were cosegregated with dyslexia in affected Norwegian samples[56]. Petryshen and his colleagues[57] replicated this result in independent samples of Canadian origin. Multipoint variance component linkage analysis shows maximum LOD score of 3.82 between D2S2352 and D2S378 for spelling, 1.13 at D2S378 for phonological coding and 1.02 at D2S378 for phonological awareness. Quantitative association analysis in 119 nuclear twin-based families showed linkage to 2p12-16 for reading-related measures. The possible candidate genes present within this region are semaphorin4F (*SEMA4F*), *OTX1* and *calcineurin B*. The single nucleotide polymorphisms in *SEMA4F* and *OTX1* showed no quantitative association with dyslexia[58]. Genome wide scan by Kaminen *et al.*[59] with 376 markers suggested linkage to 2p11 and the highest NPL score of 2.55 for marker D2S2216. Parametric analysis showed LOD score of 3.01 for marker D2S286.

Chromosome 3

Linkage analyses of genome scan data from 140 families show dyslexia locus on 3p12–q13, which cosegregates

Table 1. Summary of genetic linkage studies on dyslexia. These studies have identified possible dyslexia loci on chromosome 1, 2, 3, 6, 7, 15, 18 and X

Dyslexia phenotype	Sample size	Genetic method and markers used	Locus	Reference
Dyslexia	9 families with 3 generations	Linkage Rh marker, FUCA1, D1S165	1p34–p36	54
Dyslexia	1 family (3 individuals)	Cytogenetic analysis	Translocation, 1p22;2q31	73
Phonological decoding (PD)	8 families	Linkage D1S199	1p22	55
Phonemic awareness (PA), PD, spelling, word reading	One large family with 36 members	Genome scan D2S2183, D2S393, D2S378	2p15–p16 (DYX3)	56
Phonological coding (PC)	96 Canadian families, 877 individuals	Linkage D2S2352, D2S2183, D2S2279	2p15–p16	57
Dyslexia	119 families	Quantitative association analysis D2S337-D2S286	2p12–16	58
PA, rapid naming (RN), verbal short-term memory (VSTM).	11 families, 38 subjects	Genome wide scan D2S337, D2S2368, D2S286, D2S2333, D2S2216, D2S160	2p11	59
PA, VSTM, rapid naming	140 families	Genome wide scan D3S2454, D3S3039, D3S1595, D3S3655	3p12–q13 (DYX5)	51
Dyslexia	18 US families	Linkage, sib pair analysis BF, 2C5	6p	60
Reading comprehension, reading recognition, spelling	114 US sib pairs, 50 DZ twins	Linkage, sib pair analysis D6S105, TNFB	6p21.3–p23 (DYX2)	61
PA, PD, single word reading (SWR), RN	6 families (94 individuals)	LOD-score and nonparametric analysis D6S109, D6S461, D6S299 D6S464, D6S306	6p23–p21.3	49
PD, PC, orthographic coding (OC), single word reading	82 UK families (181 sib pairs)	Linkage, sib-pair analysis F13A1, D6S89, D6S299, D6S105, TNFB, D6S291, GLP1R	6p21.3	53
PA, PD, OC	79 US families, (126 sib pairs)	Linkage, sib-pair analysis D6S461, D6S276, D6S105, D6S306, D6S258	6p23–p21.3	2
PA, single word reading, vocabulary and spelling	8 multiplex US Families (171 individuals)	LOD-score and nonparametric analysis D6S109, D6S461, D6S299, D6S464, D6S306	6p21.3	62
OC, PA, spelling, word recognition	104 families 392 individuals	Linkage D6S461	6p21.3-22	63
Spelling, PC	96 Canadian families, at least 2 affected	Linkage, sib pair analysis D6S254, D6S965, D6S286, D6S251	6q13–q16.2	65
PA, RN, VSTM	11 families 38 subjects	D7S486, D7S2847, D7S530 D7S640, D7S684	7q32	59
Reading disability	9 US families (84 individuals)	Linkage	15p	66
Dyslexia	18 families	Linkage, sib pair analysis Ynz90	15q15-qter	60
SWR	6 multiplex families (94 individuals)	Linkage D15S143	15q21	49
Spelling	7 German multiplex families (67 individuals)	LOD-score and nonparametric analysis D15S143, D15S132	15q21	9
Dyslexia	178 parent proband trios UK	Family-based association mapping D15S994, D15S214, D15S146	15q21	69
PA, RN, VSTM, reading comprehension	2 families	Cytogenetic analysis (FISH), break points between D15S143 and D15S1029	Balanced translocation t(2; 15)(q11; q21, t(2;15)(p13; q22)	70
SWR, OC, PA	195 sib pairs UK 180 sib pairs US	QTL-based genome scan D18S53-D18S64	18p11.2	72
SWR, OC, PA	195 sib pairs UK	QTL based genome scan	Xq26	72

with dyslexia. The inheritance pattern is found to be autosomal dominant and parametric multipoint analysis showed, LOD score of 3.84. This locus is named as *DYX5*. 5 hydroxy-tryptamine receptor 1F gene (*5HT1F*), a probable candidate gene, is mapped to this region which is expressed in the brain with a role in learning and memory. But the analysis shows no sequence change in affected persons[51].

Chromosome 6

Many independent linkage studies provide converging evidence that a region on 6p21.3 influences various dyslexia spectrum processes and the locus is now called *DYX2*, which is one of the most replicable findings in the genetics of dyslexia. Linkage studies in US dyslexic families revealed linkage to the markers which are just proximal to HLA region[60] on chromosome 6p21.3. This became an important finding because of the association between immunological disorders and dyslexia[13,14]. Cardon *et al.*[61] confirmed this linkage result, suggesting that the HLA region might possess the candidate gene and found that dyslexia is inherited as autosomal dominant pattern. It has been reported that significant evidence exists for linkage of phonological awareness, single word reading, vocabulary and spelling and markers located distal to D6S105/TNFB, thus providing replication of the above results[49,62]. Multipoint QTL linkage analyses in British dyslexic families suggested linkage of phonological and orthographic components and spelling to 6p markers, which is distal to HLA region[2,53]. To define more accurate location, size and peak of association of *DYX2*, Kaplan *et al.*[63] analysed 104 families with 29 markers spanning 9 Mb of 6p21.3–22. Linkage analysis showed strong evidence for linkage to 6p for all reading-related phenotypes ranging within 4 Mb region surrounding JA04. In another study, Field and Kaplan[64] could not find linkage between dyslexia phenotypes and 6p markers, but found evidence for a new locus predisposing to phonological coding deficit[65] on 6q13–q16. This suggests that more studies are required to determine the reason for the conflicting results.

Nineteen genes are already mapped to *DYX2* locus (*RU2AS*, *MRS2L*, *GPLD1*, *SSADH*, *KIAA0319*, *TRAF*, *HT012*, *FLJI2619*, *Geminin*, *KIAA0386*, *Cyclophilin A*, *CMAH*, *NUP50*, *RPS10*, *FLJI2671*, *UBE2D2*, *AP3*, *Cytokeratin8* and *P24*) and the genes *P24*, *SSADH*, *GPLD1*, *KIAA0386*, *KIAA0319* which are mapped to 6p22.3 near the marker JA04 (G72384) are highly expressed in the brain, some of which might contribute to dyslexia[66].

Chromosome 7

Genome wide scan with 376 markers in 11 families suggests a new locus on 7q32 close to *SPCH1* locus with highest NPL score of 2.77 for marker D7S530, which maps 15 Mb from *FOXP2* gene. This gene is associated with language disorder[67]. The coding region of *FOXP2* was sequenced from six dyslexic subjects, but no sequence change was found. However, 7q31–q32 contains several other genes which are expressed in brain; therefore they may have a role in dyslexia[59].

Chromosome 15

Studies of dyslexia in nine US families found linkage of reading and spelling disorder to centromeric region of chromosome 15 in about 20% of dyslexia families studied, with an autosomal dominant inheritance. Further, the spelling disability was mapped on 15q and this locus[68] is called *DYX1*. Grigorenko and colleagues[49] reported linkage for single word reading to 15q21 with LOD score of 3.15. Later, Schulte-Körne *et al.*[9] reported supportive evidence for linkage between a spelling component of reading disability and 15q markers. Family-based association mapping with two independent samples of 178 parent-proband trios provides highly significant association between reading disability and a three-marker haplotypes[69] on chromosome 15q. The location of candidate gene in the region 15q15–q21 is within 1 cM between D15S994 and D15S146. This association of dyslexia with markers is slightly proximal to this translocation breakpoint reported by Nopola-Hemmi *et al.*[70]. Most recently, a new gene *DYX1C1* was reported near the *DYX1* locus on chromosome 15q21. It is found that this gene is disrupted by translocation (2; 15)(q11; q21), which cosegregates with dyslexia. DYX1C1 protein has 420 amino acids and it is expressed in brain, lungs, kidney and testis. In the brain, it has been localized in the cortical neurons and white matter glial cells. Sequence analysis shows two SNPs, one in the transcription initiation sequence and Elk-1 transcription factor binding site and the other in the coding region. Screening of *DYXIC1* gene in other dyslexic patients shows eight polymorphisms and only two SNPs – 3A and 1249T showed association with dyslexia[71].

Chromosome 18

Fisher *et al.*[72] presented two complete QTL-based genome-wide scans in large samples of dyslexia families from the UK and the US. Single-point analysis detected linkage to marker D18S53 for single-word reading. Multipoint analysis also gave increased evidence of 18p11.2 linkage for single-word reading. Measures related to orthographic and phonological processing and phoneme awareness also showed linkage at this locus, which suggests this QTL is probably a general risk factor for dyslexia, influencing several reading-related processes.

Chromosome X

Multipoint QTL analysis of X-linked markers also suggested a locus on Xq26, which indicates that there may be higher incidence of dyslexia in males than females[72].

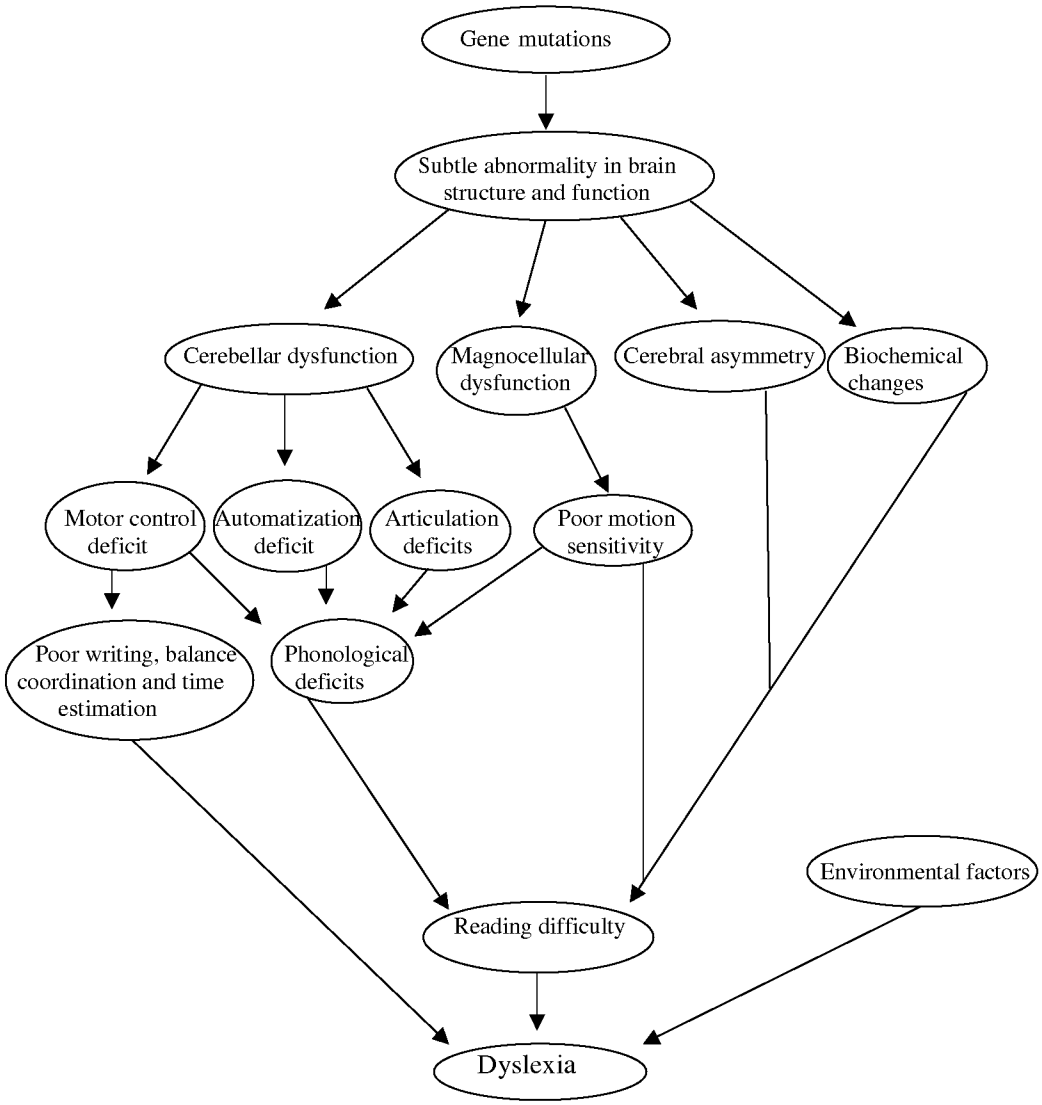

Figure 1. Schematic representation of possible pathways which lead to dyslexia. This summarizes relation between neurological and genetic pathways which lead to dyslexia. About 40% of our genes code for brain development. As the genes play an important role in brain development, defective gene products can cause deviation in the structure and function of the brain. Dyslexia is caused by anatomical and functional differences in the brain and such disturbances in turn cause reading-associated difficulties in dyslexics.

Chromosomal anomalies associated with dyslexia

Lubs *et al.*[48] show that six out of seven dyslexic family members have a translocation with the centric fusion of chromosomes 13 and 14. It is noted that a balanced chromosomal translocation, t(1; 2) (p22; q22) is cosegregating with spelling and reading disorder and delayed speech development[73]. A study performed among Finnish dyslexic families indicated that a balanced translocation, t(2; 15)(q11; q22) cosegregates with dyslexia in two families[70]. FISH analysis shows that breakpoint occurs at 6–8 Mb between markers D15S143 and D15S1029 which overlap with *DYX1* locus and this supports a putative region on 15q21.

In summary, many genetic studies have identified specific chromosomal loci for different dyslexia-related phenotypes, which suggests many genes are contributing to the predisposition of dyslexia. Loci on 6p21.3, 15q15–q21 and 18p11.2 have been identified as promising candidate gene regions[66,71,72].

Comprehensive model to explain the causes of dyslexia

Dyslexia is a complex disability which affects different aspects of reading. Acquisition of reading-related skills are coordinated by visual, motor, cognitive and language areas of the brain. Thus dyslexia can result from deviation of normal anatomy and function of those areas in the brain. Any anatomical and functional changes in the brain can be attributed to genetic variants and they can be produced by mutation(s) in the gene/s at different protein domains. These genetic variants, often in association with

environmental factors, hinder normal development of reading-related areas of the brain, which in turn brings defective reading phenotypes (Figure 1).

Conclusion

Even though interest and knowledge about dyslexia is increasing, decades of multidisciplinary research in this area in different parts of the world does not provide proper diagnostic criteria. In this regard, genetic analysis promises some insights into the problem. Several phenotypes have been found in dyslexia, but the etiological link between these related phenotypes and genotype is yet to be established. Much study is needed in this area to prove a definitive relationship between phenotype and genotype of dyslexia. Thus, isolation and analysis of the genetic variants will initiate a new phase of research which will provide a more fundamental understanding of the nature of dyslexia, eventually leading to early diagnosis, risk estimation, better methods of treatment and prevention.

Dyslexia is a major educational problem in our country and its wide presence has to be acknowledged and dealt with. Pupils with dyslexia are generally ignored and passed unnoticed in schools, until they become dropouts or delinquents. There is a great dearth of proper statistical data to show the incidence of dyslexia among pupils in India. No substantial and significant research work has been undertaken in our country in this regard. If this area is neglected any more, our country may face a high dropout rate of pupils at the elementary stage of education. There should be implementation of legislation in the country to take utmost care of these children, because dyslexia is an invisible handicap.

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