Monogenic and chromosomal causes of isolated speech and language impairment

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ABSTRACT

The importance of a precise molecular diagnosis for children with intellectual disability, autism spectrum disorder and epilepsy has become widely accepted and genetic testing is an integral part of the diagnostic evaluation of these children. In contrast, children with an isolated speech or language disorder are not often genetically evaluated, despite recent evidence supporting a role for genetic factors in the aetiology of these disorders. Several chromosomal copy number variants and single gene disorders associated with abnormalities of speech and language have been identified. Individuals without a precise genetic diagnosis will not receive optimal management including interventions such as early testosterone replacement in Klinefelter syndrome, otorhinolaryngological and audiometric evaluation in 22q11.2 deletion syndrome, cardiovascular surveillance in 7q11.23 duplications and early dietary management to prevent obesity in proximal 16p11.2 deletions. This review summarises the clinical features, aetiology and management options of known chromosomal and single gene disorders that are associated with speech and language pathology in the setting of normal or only mildly impaired cognitive function.

INTRODUCTION

Over the last decade, molecular genetic testing of children with moderate to severe intellectual disability (ID), autism spectrum disorder (ASD) and epilepsy has become an integral part of the diagnostic evaluation of these children. The importance of a precise molecular diagnosis in informing the clinician about optimal management, prognosis and genetic counselling is widely accepted.[1] Speech and language abnormalities frequently co-occur with these developmental disorders and as a result, clinical geneticists are frequently asked to assess children with speech and language difficulties. Severe language delay is also a symptom of several well recognised genetic conditions presenting to clinical geneticists such as Pitt-Hopkins syndrome and Angelman syndrome (AS).[2 3] In contrast, children with an isolated speech or language disorder are not often genetically evaluated, despite recent evidence supporting a role for genetic factors in the aetiology of these disorders.[4–9]

Several types of speech and language pathology have been described although nomenclature is somewhat variable (for a summary of useful definitions see online supplementary appendix).[10 11] In general, speech disorders include voice problems and/or the inability to produce speech sounds correctly or fluently. Language disorders include expressive and receptive language disorders. Children with an expressive language disorder are more able to understand language than they are to express themselves with language. Such children also frequently have receptive language delay; difficulties understanding language. Expressive and receptive language delay can occur separately or together in an individual and either can be isolated or occur as part of a broader developmental problem.

During the past few years, advances in genetic technology have led to the identification of several chromosomal CNVs and single gene changes associated with abnormalities of speech and language. A major drawback of many of these reports is the lack of a standardised description of the type of speech/language disorder reported. As a consequence, the potential relevance of these reported genetic alterations to the causation of speech/language disorders is often not highlighted in the literature. Furthermore, in contrast to genetic syndromes, disorders of speech/language may be overlooked as they often present without clearly defined clinical features. This is particularly true when speech or language problems are the main presenting symptom in a child who has only mild developmental delay or otherwise normal development. Individuals without a precise genetic diagnosis are less likely to receive optimal management including beneficial treatment interventions. This review summarises the clinical features, aetiology and management options of known chromosomal (table 1) and single gene disorders (table 2) that are associated with speech and language pathology which can occur in the setting of normal or only mildly impaired cognitive function.

METHODS

Selection criteria

This review aims to report on monogenic and chromosomal disorders involving speech and language pathology. Information on chromosome and single gene disorders associated with developmental speech and language problems was extracted from PubMed using search terms 'speech', 'language', 'chromosome' and 'mutation'. Genome wide association studies were excluded from this review. In addition, to prevent bias towards specific types of speech and language pathology we did not extend the search to terms indicating (sub)types or symptoms of speech and language pathology (eg, search terms such as dysarthria, apraxia, stuttering, phonation deficits were not used).

In addition, this report aimed to focus on primary speech and language pathology, which we define as speech and language pathology occurring in the setting of normal or only mildly impaired cognitive function. The reason for this focus is that historically genetic testing has often not been

Table 1 Chromosomal aberrations that are associated with speech and language pathology and can occur in the setting of normal or only mildly impaired cognitive function

Chromosome disorder (name syndrome)	Chromosome position (Hg19) and major candidate genes phenotype	Clinical features	No. of publ. cases	Considerations for medical follow-up*
1p21.3 microdeletion	Chr 1: 97.5–98.5 Mb *DPYD* and *MIR137*	Normal IQ-mild ID, severe speech delay, ASD	<20	Counselling carrier status dihydropyrimidine dehydrogenase deficiency
7q11.23 microduplication (OMIM 609757)	Chr 7: 72.8–74.3 Mb *GTF2I*	Normal IQ-moderate ID, dysmorphia, hypotonia, severe expressive language delay, dysarthria, aortopathy	>75	Cardiac evaluation
10q22q23 microdeletion	Chr10: 81.6–89.1 Mb	Borderline-moderate ID, expressive/ receptive language delay, macrocephaly, dysmorphia, cardiac anomalies, cerebellar anomalies	<20	Cardiac evaluation and GI follow-up
12p12.1 microdeletion (OMIM 604975)	Chr 12: 23.7–24.7 Mb *SOX5*	Normal IQ-moderate ID, expressive language delay, mutism, ADHD, aggression	<20	–
12p13.33 microdeletion	Chr12: 1.1–1.6 Mb *ELKS/ERC1*	Normal IQ-mild ID CAS, ADHD, DD	<20	–
15q11.2 microdeletion (OMIM 615656)	Chr15: 22.8–23.1 Mb *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5*	Normal IQ-mild ID Speech and language delay, ADHD, ASD, epilepsy, CHD	>100	Cardiac evaluation
15q11.2q13 microduplication (OMIM 608636)	Chr15: 23.1–28.9 Mb	Normal IQ-moderate ID, parent of origin effect, speech delay, apraxia, dyslexia, motor delay, hypotonia, ASD	>75	Awareness and treatment of GI symptoms
Proximal 16p11.2 microdeletion (OMIM 611913)	Chr16: 29.5–30.3 Mb	Normal IQ-moderate ID, speech/language delay, obesity, CAS, congenital abnormalities	>75	Dietary management
17p11.2p11.2 microduplication (Potocki-Lupski syndrome) (OMIM 610883)	Chr 17: 16.8–20.3 Mb	Low-average IQ-moderate ID, speech/language delay, ASD, hypotonia, feeding difficulties, behavioural problems, CHD, aortopathy	>75	Cardiac evaluation, assessment of sleep apnoea
22q11.2 microdeletion (velocardiofacial syndrome) (OMIM 192430)	Chr 22:18.7–21.8 Mb *TBX1* and *COMT*	Normal IQ-mild ID, speech/language delay, CHD, velopharyngeal insufficiency, cleft palate, hypotonia	>100	Multiple medical recommendations: see published guidelines [12–14]
22q11.2 distal microdeletion (OMIM 611867)	Chr22: 22.1–23.8 Mb	Normal IQ-mild ID, hearing loss, speech/language delay, gross delay, behavioural problems, CHD	>25	Hearing assessment, cardiac evaluation
Sex chromosome aneuploidy	47,XXY 47,XYY 47,XXX 45,X†	Average IQ/mild DD, ADHD, features of hypogonadism Average IQ/mild DD, ADHD Average IQ, mild DD, ADHD Average IQ, features of ovarian dysgenesis	>100 >100 >100 >100	Multiple medical recommendations: see published guidelines[15] – – See published guidelines[16]

*Medical surveillance to consider in addition to speech/language evaluation and therapy.
†In general, individuals with Turner syndrome have average to above average performance on most verbal tasks, however there is evidence that oral fluency skills are impaired.
ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CAS, childhood apraxia of speech; CHD, congenital heart disease; DD, developmental delay; GI, gastrointestinal; ID, intellectual disability; No., number; publ, published.

performed in these individuals because of the lack of clear comorbidities such as cognitive impairment, dysmorphism or congenital anomalies. Disorders have only been selected under the condition that normal or borderline intellectual function has been reported as part of the cognitive spectrum. Disorders lacking literature descriptions of individuals with normal/borderline cognitive function were excluded from this review.

Chromosomal disorders

CNVs include deletions and duplications on chromosomes and are a common type of genomic variation. Copy number changes may range in size from a kilobase (kb) to several megabases (Mb) or even a whole chromosome (trisomies and monosomies) and may comprise one or more genes.[1] CNVs can be detected using genomic microarrays, which are often used as a first-tier test in the evaluation of individuals with developmental delay, autism, epilepsy and/or congenital anomalies. Clinical interpretation of rare CNVs still remains challenging as many CNVs are rare and non-recurrent and large cohort studies of healthy control individuals have shown that each person carries multiple, most often benign, CNVs.[1] In general, interpretation of the causality of a CNV in an affected individual is based on its frequency in healthy control individuals, the inheritance pattern in the respective family, the presence of overlapping aberrations in patients with similar phenotypes and the CNV characteristics such as size, copy number state (gain or loss) and gene content.[17] Nevertheless, rare CNVs that are inherited from healthy parents may remain difficult to interpret as variable expressivity and decreased penetrance may occur.[17] The CNVs included in this review have all been reported as pathogenic, yet penetrance and expressivity may still be variable for each of these disorders. Smaller CNVs located within or only partly overlapping these genomic regions may still be of a benign nature. A CNV may result in disruption of gene structure or change in gene dosage. Where known, information on candidate genes underlying the phenotypical features is discussed.

Table 2 Single gene disorders that are associated with speech and language pathology and can occur in the setting of normal or only mildly impaired cognitive function

Gene (name disorder)	Chromosome position (Hg19)	Clinical features	No. of publ. cases	Considerations for medical follow-up*
FOXP2 (OMIM 602081) *(Speech and language disorder 1)*	Chr 7: 113.7–114.3 Mb	Normal IQ-mild DD, severe speech delay, verbal dyspraxia	>25	–
SETBP1 (OMIM 611060)	Chr 18: 42.3-42.6 Mb	Normal IQ-severe ID mutism, severe speech delay	<10	–
TM4SF20 (OMIM 615432)	Chr 2: 228.2–228.2 Mb	Normal IQ, speech delay, white matter hyperintensities	15 families	–
FMR1 (OMIM 309550) (Fragile X syndrome in women)	Chr X: 147.0–147.0 Mb	Normal IQ-moderate ID, speech delay, POI and FXTAS	>100	Reproductive endocrine evaluation and treatment supportive care for gait disturbances
GALT (OMIM 606999) (Treated classic galactosaemia)	Chr 9: 34.6–34.7 Mb	Normal IQ-borderline ID, vocabulary and articulation problems, CAS and dysarthria, motor disturbances, POI	>100	Galactosaemia treatment from birth onwards Reproductive endocrine evaluation and treatment
NRXN1 (OMIM 600565)	Chr 2: 50.1–51.3 Mb	Normal IQ-DD, ASD, speech and language delay, CHD, epilepsy	>75	Cardiac evaluation
GRIN2A (OMIM 138253) (Landau-Kleffner syndrome)	Chr 16: 9.8–10.3 Mb	Normal IQ-mild ID, dyspraxia, impaired motor planning and programming and dysarthria, epilepsy	>50	Epilepsy monitoring and treatment

*Medical surveillance to consider in addition to speech/language evaluation and therapy.
ASD, autism spectrum disorder; CAS, childhood apraxia of speech; CHD, congenital heart disease; DD, developmental delay; FXTAS, fragile-X associated tremor/ataxia syndrome; ID, intellectual disability; No., number; POI, primary ovarian insufficiency; publ, published.

1p21.3 deletion

Less than 10 individuals with a deletion of chromosome 1p21.3 including *DPYD* and *MIR137* have been reported.[18 19] They showed severe speech delay, features of ASD, normal gross motor development and absence of major medical problems. Cognitive function varied between IQ in the normal range and borderline-mild ID. Several individuals showed a discrepancy between verbal and performance IQ with a relatively low score on verbal capacities. Speech deficits included poor intelligibility and pronunciation difficulties. There is at least one report of an intragenic deletion in *DPYD* in a patient with speech delay and autism, suggesting that *DPYD* is a candidate gene for speech delay.[18] Point mutations and intragenic deletions in *DPYD* confer carrier status for dihydropyrimidine dehydrogenase deficiency. Recently, a rare variant in *MIR137* has been reported as a possible risk factor in schizophrenia and bipolar disorder.[20]

7q11.23 microduplication

Williams-Beuren syndrome (WBS) is a recognisable microdeletion syndrome, caused by a 1.5 Mb deletion at 7q11.23.[21 22] WBS is characterised by a typical facial gestalt, supravalvular aortic stenosis, infantile hypercalcaemia and a specific cognitive profile. The reciprocal duplication was first reported in 2005.[8] This boy showed mild developmental delay, severe expressive language impairment, hypotonia and mild dysmorphic features. These features have subsequently been confirmed as common features of this duplication in large cohorts.[23 24] In contrast to WBS, characterised by fluent expressive language, duplication carriers show impaired expressive language characterised by oral motor problems and speech sound delays and disorders.[25] Children have been reported with mixed motor speech disorders including childhood apraxia of speech (CAS), dysarthria, phonological disorder and/or oral apraxia.[25] Although the majority of carrier adults also showed symptoms of these disorders, none of them showed enough symptoms to meet the criteria to be diagnosed with a speech disorder.[25] The intellectual abilities of children with this microduplication varied from mild-moderate ID to average for the general population.[25] Most duplication carrier parents showed a history of learning difficulties and/or language delay but were employed and functioning well in adult life.[23 24] Due to the finding of cardiac defects and aortopathy in a subset of individuals, cardiovascular surveillance has been recommended for these patients.[26] Minor dysmorphic features, neonatal hypotonia, various brain anomalies, cleft palate, epilepsy, cryptorchidism, joint laxity, attention-deficit hyperactivity disorder (ADHD) and autistic features have also been reported in some individuals.[23 27] One study reported separation-anxiety disorder in 30% of 4–12-year-old individuals with a duplication. The *GTF2I* gene has been suggested as the most important gene contributing to the cognitive phenotype in WBS.[28] An extra copy of *Gtf2i* in mice leads to increased separation-induced anxiety in these animals, suggesting an important role of *GTF2I* in this phenotype.[29]

Deletions of chromosome 10q22q23

Deletions of chromosome 10q22q23, between two low copy repeats (LCR3 and LCR4), lead to borderline-moderate cognitive impairment with apparent speech and language problems.[30–32] Motor developmental delay may also occur, although speech seems more severely affected. The majority has expressive and receptive language problems. In addition, auditory language processing, speech impairment and mild oral motor deficits have been reported. Macrocephaly, mild facial dysmorphisms (broad forehead, deep-set eyes, upslanting palpebral fissures, a smooth philtrum and a thin upper lip), cerebellar anomalies, cardiac defects and congenital breast aplasia have been described.[30] Parental inheritance with segregation of the phenotype has been reported.[31] Cardiac evaluation in newly diagnosed individuals is recommended as cardiac anomalies such as persisting ductus arteriosis, atrioventricular septal defects and tricuspid and pulmonic regurgitation have been reported. Mutations and exonic deletions in *BMPR1A* are associated with juvenile polyposis syndrome (JPS).[33] So far, no polyps have been reported in LCR3-LCR4 10q22q23 deletion

carriers. However, the majority of carriers have been described before the age of 12 years. Symptoms of JPS, such as rectal bleeding, usually present in older children and young adults. Colorectal cancer as a result of transformation of these polyps usually does not occur until the fourth decade and does not occur in all individuals with JPS.[34] Therefore, appropriate gastrointestinal (GI) follow-up from 15 years onwards may be considered.[32]

Deletions of 12p12.1

Deletions of 12p12.1 including the translated region of *SOX5* are associated with developmental delay with prominent language delay without specific associated physical abnormalities.[35–37] Average intellectual development has been reported in a patient with an atypical deletion limited to the untranslated region of *SOX5*, but most individuals show borderline, mild or moderate intellectual impairment. All individuals with alterations of *SOX5* have been reported with a predominantly expressive language disorder. Complete absence of language has occasionally been reported. Other features included poor articulation and dyspraxia. Behaviour problems included aggressive behaviour, self-injurious behaviour and ADHD.[37]

Deletions of 12p13.33

In most carriers of a 12p13.3 deletion the first symptom was speech delay, with first words at around 36–40 months.[38] In some, walking development was also delayed. All individuals who were available for professional assessment by a speech pathologist could be diagnosed with CAS. Deletions were inherited from a parent in around half of the cases. Variable expression within families has been reported. The majority showed borderline-mild ID. Some individuals had a normal IQ. However, retrospective interviews revealed all had speech delay and learning difficulties during childhood and none of them graduated secondary school. ADHD and behaviour problems have been frequently reported. The *ELKS/ERC1* gene has been proposed as the best candidate gene as it is the only gene located in the smallest region of overlap in all individuals with 12p13.33 deletions and speech delay.[38]

Deletions of 15q11.2

The proximal 15q region is characterised by a high density of segmentally duplicated blocks.[39 40] Speech and language and motor developmental delay are common in individuals with deletions of chromosome 15q11.2 between the first pair of segmentally duplicated blocks adjacent to the Prader-Willi syndrome and AS critical region.[41–43] The possible involvement of this region in speech impairment has also been shown in a study reporting an increased absence of vocalisation in AS individuals that carry the larger deletion including this proximal region.[44] The 500 kb region includes four non-imprinted genes, *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5*. Three of these genes are implicated in central nervous system development and/or function.[42 45] Most individuals show normal development or only mild cognitive impairment.[41] Speech delay has been reported in the majority of individuals although formal speech and language assessment studies would be useful to further specify these findings.[41–43] Behaviour issues including ADHD or ASD, epilepsy and congenital heart disease have also been reported in a subset of individuals.[43 46] The latter may be underestimated as most individuals do not come to the attention of a physician due to the mild phenotype. Therefore echocardiographic examination has been recommended for these individuals.[43]

15q11.2q13 microduplication

Similar to the reciprocal 15q11.2q13 deletion in Prader-Willi syndrome and AS there are two types of aberrations. Type I duplications occur between segmentally duplicated blocks BP1 and BP3 and type II duplications between BP2 and BP3.[47] Despite the uniformity of the duplication sizes, the phenotype may be highly variable, even within the same family.[48] Paternal origin of the duplication is usually associated with a normal or mild phenotype.[49] The level of intellectual functioning varies from normal development to marked cognitive impairment.[50–52] Speech delay is reported in the majority of individuals. In one family with multiple affected individuals formal language assessment revealed apraxia of speech, phonological awareness deficits, developmental language disorder, dyslexia and limb apraxia.[48] In another study receptive language difficulties were reported.[50] Additional frequently reported features include motor delay, hypotonia, joint laxity, autism and GI problems.[51–53] The latter include reflux and constipation in the majority of cases.[53] Behaviour problems, possibly caused by GI related discomfort, have been reported to improve with treatment of GI symptoms in several individuals. However, GI problems may be difficult to diagnose in individuals with severe speech and language difficulties warranting increased awareness for early diagnosis and treatment. Most common treatments were stool softeners and stimulants such as polyethylene glycol and bisacodyl for constipation and proton pump inhibitors for reflux. In most cases, major dysmorphisms or congenital anomalies are absent.[51 52]

Proximal 16p11.2 microdeletion

Recurrent proximal deletions at 16p11.2 have been associated with intellectual impairment, speech and language delays, autism and obesity.[54–56] Early diagnosis and dietary management may help to prevent excessive weight gain/obesity.[57] The frequency of this deletion may exceed 1:5000 and is found in approximately 0.5% of all samples tested clinically.[55 58] The role of this genomic region in speech/language development has been confirmed by several studies. In one study (n=9 individuals) reporting on developmental milestones for speech-language acquisition 67% had significant delays in age of single word acquisition, 78% had delays in age of phrase development and all had deficits in reciprocal conversation.[59] Recently, carriers of a 16p11.2 deletion with CAS have been reported.[59 60] Three studies on large cohorts of carriers and intrafamilial non-carrier controls showed that relative to family members without the deletion carriers showed a 1.7–2 SD decrease in IQ.[61–63] Among carriers of one of these studies, 20% met Diagnostic and Statistical Manual V-Text Revision (DSM V-TR) criteria for ID (65% mild and 35% moderate).[61] A consistent deficit in expressive and receptive spoken language and articulation could be observed.[61] Verbal IQ (mean 74) was lower than non-verbal IQ (mean 83) and the majority of carriers required speech therapy.[62] ASD could be diagnosed in 15–24% of all individuals.[61 62] In addition, other psychiatric disorders or autism-related traits were noted in the majority of individuals. A recent study showed that despite large deleterious effects, there is a significant positive correlation between the full-scale IQ, verbal IQ and social responsiveness scale between parents and probands with a de novo deletion. These results indicate that family background has a strong contribution to the phenotypical variability of this genomic disorder.

Recently, an adjacent non-overlapping 16p11.2 deletion involving the *SRCAP* gene was described in a girl with severe speech impairment and behaviour problems. Her IQ was tested in the normal range.[64] No additional individuals with similar

deletions have been reported yet, and therefore this deletion has not been included as a separate disorder.

17p11.2 duplication

Potocki-Lupski syndrome is caused by duplication of chromosome 17p11.2 and is the reciprocal product of the Smith-Magenis syndrome microdeletion. Except for a minority with low-average to borderline intellectual function, most individuals show intellectual impairment in the mild-moderate range. Other features include significant speech and language delay, autism, hypotonia, prominent sucking/feeding difficulties, behaviour problems, sleep apnoea and cardiovascular anomalies such as structural heart disease, aortopathy and ECG anomalies.[65–68] Therefore individuals with Potocki-Lupski syndrome should be evaluated and monitored by ECG and echocardiography.[68] In addition, assessment of sleep-disordered breathing may be considered.[66] Most cases are sporadic, but familial transmission has been observed in a few families.[69 70] Speech and language impairment is a consistent finding, regardless of the level of cognitive and social functioning. A better non-verbal function compared with verbal function, apraxia of speech and expressive and receptive language difficulties have been observed.[66 71] A small study reported echolalia, intonation and rhythm abnormalities, the usage of pedantic language, running commentaries and reference to themselves in the third person.[67]

22q11.2 microdeletion syndrome

Different classifications, such as velocardiofacial syndrome, Shprintzen syndrome and DiGeorge syndrome, are all presentations of 22q11.2 deletion.[72] Common features include mild developmental delay (mean IQ in the low 70s, 30% between 80 and 100), speech and language problems, velopharyngeal insufficiency, cleft palate, hypotonia, constipation, conotruncal cardiac malformations and thymus and parathyroid hypoplasia. In addition, patients may have seizures, abnormal hearing, urogenital anomalies, psychiatric illness, behavioural problems and dysmorphisms.[12 73–75] Clinical guidelines for evaluation and therapeutic management of children and adults with 22q11.2 deletion syndrome are useful to tailor clinical care during different stages of life.[12–14] The estimated frequency varies from 1:4000 to 1:6395.[76 77] In 8–28% of cases the deletion is inherited from a parent.[74 78 79] Speech and language delay has been observed in 70% of individuals during follow-up.[80] Significant discrepancy between receptive and expressive language has been reported.[7] Phonation defects due to velopharyngeal insufficiency and hearing difficulties influence language acquisition in many patients.[80] Therefore, otorhinolaryngological and early audiometric evaluation has been recommended.[80] Deviant articulation and reduced intelligibility has been reported to improve significantly with age.[81] However, persistent problems with velopharyngeal impairment have been noted.[81] *TBX1* and *COMT* have been suggested as candidate genes for the neurocognitive and anatomical abnormalities that lead to speech disturbance in 22q11.2 microdeletion syndrome.[82]

22q11.2 distal microdeletion

Distal 22q11.2 deletions, located between segmental duplication blocks LCR22-4 to LCR22-5 or LCR22-6, represent a different clinical phenotype compared with more proximal deletions associated with the well known DiGeorge/velocardiofacial phenotypes.[83–86] Most deletions occur de novo, but inheritance has also been reported.[87 88] Cognitive function in individuals with this deletion varies from normal to mild cognitive impairment with a significant language delay component.[87 88] Several patients with hearing impairment have been reported, warranting evaluation to optimise conditions for development.[87] Except for single case descriptions of affected speech and language, further studies are needed to increase insight in the associated speech and language pathology. Commonly noted other features include prematurity, growth retardation, behavioural problems, truncus arteriosus, variable minor skeletal abnormalities and subtle facial dysmorphisms.[83 84 87] Larger deletions, also including the region between LCR22-6 and LCR22-7 harbouring the *INI1 (SMARCB1)* gene, have been associated with an elevated risk of developing rhabdoid tumours.[89]

Sex chromosome aneuploidies

The sex chromosome trisomies include Klinefelter syndrome (47,XXY; 1.72:1000 men), XYY syndrome (47,XYY; 1:1000 men) and triple X syndrome (47,XXX; 1:1000 women).[90] Although most adults with sex chromosome trisomies live independent lives, they have been associated with significant language and reading problems.[5 9 91] A poor verbal ability and behavioural and social difficulties have been reported.[91] In a recent study, which investigated the prevalence of sex chromosome aneuploidies within a group of children and young adults with language and reading problems, aneuploidies were found in 2.9–3.4% of probands with oral speech and language deficits compared with an expected population frequency of 0.25%.[9] Due to decreased awareness among health professionals Klinefelter syndrome remains undiagnosed in up to 75% of individuals.[15] Early detection of this syndrome is important to offer appropriate management at the correct ages and stages of development to decrease potential learning and psychosocial problems, to prevent osteopenia and osteoporosis, metabolic syndrome and other medical conditions related to hypogonadism.[15] These now include evidence that early (age 15–17 years) sperm retrieval in men with Klinefelter syndrome can result in successful pregnancy via in vitro fertilisation in the future.[92] Guidelines summarising the clinical features and the various options for treatment and intervention are available to diagnose this syndrome as early as possible and to optimise care for these individuals.[15] Klinefelter syndrome presents with global delays in speech from early development and up to 80% of individuals present with, mainly language related, learning disabilities during childhood.[93] Most severe deficits include encoding of verbal information, auditory processing, comprehensions and processing speed. Expressive speech and verbal fluency are also affected. Overall intellectual function is in the average to low-average range. Nearly 50% of individuals has also been diagnosed with ADHD.[93]

Verbal impairments in XYY syndrome are comparable to Klinefelter syndrome.[93] They consist of difficulty in naming, receptive vocabulary and verbal fluency. Intelligence is within the normal or slightly low-average range.[93] Increased impulsivity and externalising behaviours have been reported and ADHD is diagnosed in up to 62% of cases.[93]

In women with triple X syndrome expressive language is more impaired compared with receptive language with a pattern described as developmental dyspraxia in some individuals.[93 94] However, impairments in expressive and receptive language have also been reported.[94] Language difficulties include language processing, verbal fluency, language comprehension and pragmatic language difficulties.[94] Average full scale IQ is between 85 and 90 with a difference between verbal and non-verbal/performance domains with main deficits in verbal function.[94] ADHD is present in 25–35% of cases.[94]

In contrast to the aforementioned sex chromosome aneuploidies, studies regarding speech and language abilities in Turner syndrome are harder to interpret.[95] Group data support the general view of normal to strong verbal abilities in these individuals.[16] However, this language strength seems not global, there is evidence that oral fluency skills are impaired despite average to above average performance on most other verbal tasks.[96 97] In addition, a retrospective study under 54 parents of individuals with Turner syndrome reported late speech and language development in 22 children.[98] Partially, this relatively high percentage may have been caused by recurrent otitis during infancy, which is a common feature of Turner syndrome. Turner syndrome occurs with an incidence of about 1/2500 women.[99] Average IQ is between 95 and 102.[95] The main features include short stature and ovarian dysgenesis. Other visceral manifestations may include lymphoedema, deafness, cardiovascular thyroid and GI involvement.[16] Guidelines for diagnosis and optimal management including growth hormone treatment are available.[16]

Single gene disorders

FOXP2

FOXP2 (Forkhead box protein P2) was the first gene associated with severe speech disorder. Mutations and gene deletions of *FOXP2* lead to developmental verbal dyspraxia with impaired expressive and receptive language.[100–102] Some individuals also show mild developmental delay. *FOXP2* was first discovered in a large three generational pedigree with multiple affected family members. Using linkage studies, a region on chromosome 7q31 was found to be segregating with the disorder.[103] A de novo balanced translocation in an unrelated child with similar speech problems subsequently pinpointed to the causative gene.[100 104] Prevalence of mutations in individuals with severe speech disorders has been estimated at 2%.[105]

The core phenotype consists of a severe motor speech disorder, with most individuals having CAS. Oral motor dyspraxia, unintelligible speech, dysarthria, impaired word reading, spelling and phonological awareness skills have also been reported[102 106 107] Receptive and expressive language is usually affected. Non-verbal performance within the normal range has been reported in some individuals and is often better compared with verbal skills.[102 106 107]

Functional cooperativity has been demonstrated for Foxp1 and Foxp2 in mouse development and an overlap in expression in the songbird and human fetal brain has suggested that *FOXP1* may also have a role in speech and language disorders.[108 109] Deletion or inactivating mutations of *FOXP1* are indeed also associated with moderate to severe speech and language delay.[110–112] In these individuals expressive language is more severely affected compared with receptive skills and they may show difficulties with articulation of consonants.[110–112] However, the majority of individuals thus far reported also show moderate ID and therefore this gene is not included as single gene disorder in table 2. Other features include facial dysmorphisms, relative macrocephaly and autistic traits.[110–112]

SETBP1

Haploinsufficiency of *SETBP1* has been postulated as the causative gene for expressive speech delay in individuals with chromosome 18q12.3 deletions.[113 114] Recently, it has been shown that disruptive mutations in *SETBP1* are indeed highly penetrant (92%) for completely absent or substantially impaired speech and language development.[115–117] Due to its strong association with speech and language development *SETBP1* might become of similar interest to the speech and language community comparable to *FOXP2*. Although the range of intellectual development ranged from normal to severe impairment in this limited amount of cases, mild ID was noted in the majority of cases. A complete lack of expressive speech with intact receptive language abilities has been noted in several individuals. In these cases active communication using gestures and mimic expression of face and body was surprisingly effective.[113–115] Other features included decreased fine motor skills, subtle dysmorphisms, hyperactivity and autistic traits.[115 116] Gain-of-function mutations of a hot spot region in exon 4 of *SETBP1* result in a clearly different and more severe phenotype, namely the Schinzel-Giedion syndrome.[118] This syndrome is characterised by profound ID, persistent feeding problems, severe forms of epilepsy, a recognisable facial gestalt, various congenital organ defects, blindness, deafness and neuroepithelial neoplasia. Most individuals die during infancy or early childhood.[118]

TM4SF20

A 4 kb deletion of *TM4SF20,* encoding a transmembrane protein of unknown function located at chromosome 2q36.3, has been reported to segregate with early childhood communication disorders and white matter hyperintensities (WMHs) in 15 unrelated families predominantly from South-East Asia.[119] This population-specific deletion, that removes the penultimate exon 3 of *TM4FS20,* is highly penetrant and segregated with familial WMHs and disorders of communication. The phenotype of the majority of children included language delay without significant dysmorphisms or other congenital anomalies and with normal motor development. Formal speech/language and development assessment showed significant discrepancies between verbal and non-verbal skills. Abnormalities consistent with WMHs were observed on brain MRIs in 69% of deletion carriers. Data from the parental carriers and extended pedigree analyses suggested that language delay convalesces over time in most individuals, potentially reflecting compensatory neuronal plasticity.[119]

Women with fragile X syndrome

Most individuals with fragile X syndrome (FXS) have a loss-of-function mutation in *FMR1* caused by an increased number of CGG trinucleotide repeats (>200) leading to abnormal methylation of *FMR1*.[120] FXS in men is associated with moderate ID, delayed speech and language development, facial dimorphisms, macroorchidism, ASD and behaviour problems.[120] In women, symptoms of FXS may be more variable in terms of behavioural and neurocognitive outcomes.[120] Adult women are at increased risk for primary ovarian insufficiency and fragile X associated tremor/ataxia syndrome.[120] Intellectual function in women may vary between normal IQ to moderate ID. Approximately 50% of women who are heterozygous for the full mutation are intellectually normal.[120] Language has been assessed in a group of girls with FXS.[121] In 40%, receptive vocabulary was well below the cut-off for language impairment. Fragile X testing should be considered in each child with delay of speech and language, especially in the presence of a family history of ID.

Treated classic galactosaemia

Classic galactosaemia is an autosomal recessive disorder caused by biallelic mutations in *GALT* (Galactose-1-Phosphate uridylyltransferase), the gene encoding galactose-1-phosphate uridyl transferase.[122] Unless a lactose-free diet is followed, classic galactosaemia leads to severe life-threatening complications

including failure to thrive, hepatic damage, bleeding and sepsis in infants.[123] Children who are treated from birth remain at increased risk for developmental delay, speech and language problems, motor disturbances and premature ovarian insufficiency.[124] Mean total IQ scores were 78 and 73 at average age 10.8 years and 25.7 years, respectively.[125] Speech problems starting in early childhood have been reported in up to two-thirds of individuals and continue into adulthood.[126] Vocabulary and articulation problems, CAS and dysarthria have been frequently noted.[122]

NRXN1

Deletion of *NRXN1* (Neurexin 1) on chromosome 2p13.3 has been associated with developmental delay, ASD, prominent speech and language delay, cardiac anomalies and seizures.[127 128] Individuals with normal intellectual function have been reported.[129] Although the phenotypical variability is large, speech delays have been noted in 78% of individuals and may also segregate in families.[129 130] Additional studies are warranted to further delineate the type of language and speech defects.

GRIN2A

GRIN2A (glutamate receptor, ionotropic, N-methyl D-aspartate 2A) mutations have been reported in individuals with epilepsy-aphasia spectrum disorders that include Landau-Kleffner syndrome, epileptic encephalopathy with continuous spike-wave in slow-wave sleep, atypical rolandic epilepsy with speech impairment and intermediate epilepsy-aphasia disorder.[131 132] In clinical practice, patients may first present with substantial language difficulties including verbal dyspraxia before developing seizures. In a few individuals the speech phenotype occurred in the absence of a seizure disorder.[133] The *GRIN2A* speech phenotype includes dyspraxia, impaired motor planning and programming and dysarthria with impairment in speech execution. Most individuals with *GRIN2A* mutations showed normal, borderline or mildly impaired intellectual function.

CONCLUSION

Molecular genetic testing should become part of the standard evaluation of children presenting with primary speech and language pathology. Unless there is a family history or a presence of clinical key features pointing towards a specific genetic disorder, genome-wide chromosome analysis with high resolution to detect CNVs is the test of first choice (figure 1). A recent study found sex chromosome aneuploidies in 2.9–3.4% of children with oral speech and language deficits compared with 0.25% in the general population.[9] Due to lack of awareness about diagnosis and management, sex chromosome trisomies remain undiagnosed in 50–90% of cases.[134–137] Early diagnosis may significantly influence psychosocial, cognitive, physiological and reproductive outcomes.[94 138] It may improve an individual's quality of life and prevent serious consequences. For example, early testosterone replacement may result in increased masculinity, strength, libido, bone mineral density and body hair in men with Klinefelter syndrome.[138] Similar examples of useful interventions following diagnosis of a chromosomal disorder (table 1) include otorhinolaryngological and early audiometric evaluation in 22q11.2 deletion syndrome, cardiac evaluation in several chromosomal disorders and early dietary management to prevent obesity in proximal 16p11.2 deletions.[30 58 80]

In case of a normal chromosomes result, monogenic causes such as *FOXP1*, *SETBP1* and *NRXN1* may be considered. Novel single gene disorders will be defined in the near future. Existing candidate genes such as *CNTNAP2*, *SRPX2* and *KIAA0319* need further study to provide substantial evidence that they are genuine monogenic causes for primary speech and language disorders.[132 139–144] Eventually, a diagnostic custom-made next generation sequencing gene panel for primary speech and language disorders may become a useful addition to the extensive range of existing gene panels in diagnostic genetic laboratories.

Finally, referral for speech and language assessment and therapy by a speech pathologist is strongly recommended for all disorders presented in this review. A lack of consistent speech/language therapy in affected children may lead to a significant discrepancy in vocabulary and grammatical abilities compared

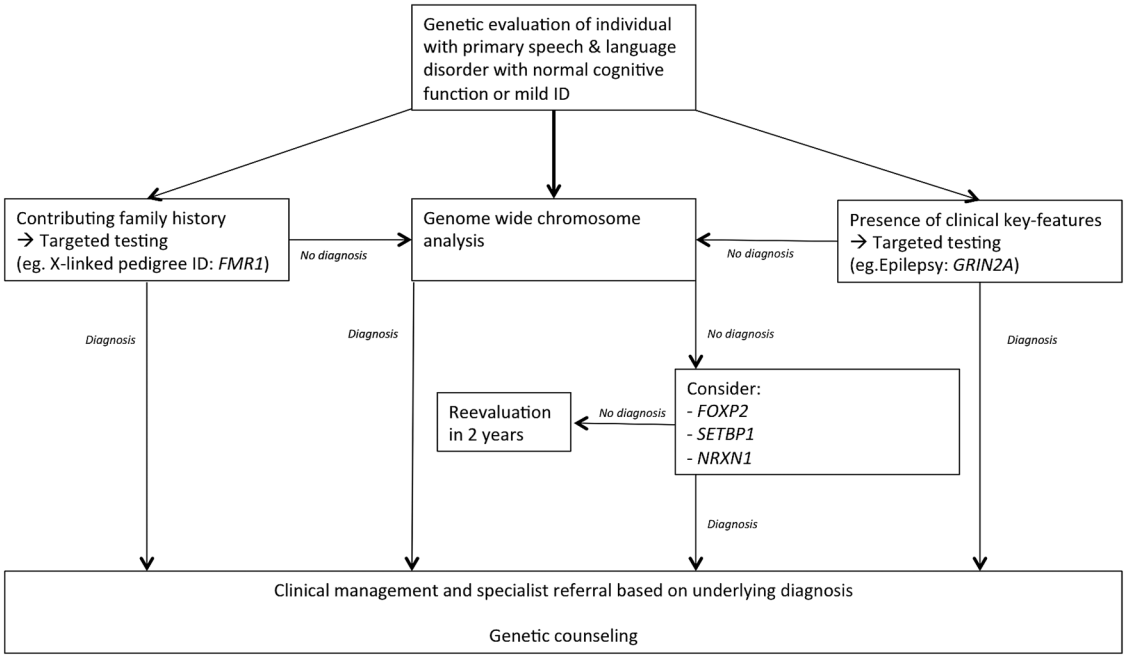

Figure 1 Diagnostic schedule for individuals presenting with primary speech and language disorder. ID, intellectual disability.

with children who have had consistent speech/language therapy from the late infant or early toddler period.[25 145] Specific speech and language interventions and augmentative communication, such as manual signing and picture-based communication, may be incorporated into children's education plans. At this stage it is not possible to provide information about tailored speech and language therapies based on the underlying disorders presented in this review. Similar to other rare genetic disorders, we are currently in an 'accumulation of knowledge phase' regarding the genetic base and exact signs and symptoms of these disorders. By defining these disorders as causes for primary speech and language pathology, we hope future studies regarding these disorders will focus more on the speech and language related signs using standardised descriptions. In this way more information will come to light and specific therapies may be developed.

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Appendix: Useful definitions for the Geneticist (adapted from American-Speech-Language-Hearing Association definitions, www.asha.org)

Speech: the verbal means of communicating. This is made up of articulation (making sounds), voice (producing sounds using the vocal folds and breathing) and fluency (rhythm of speech).

Language consists of socially shared rules that include what words mean, how to make new words, how to put words together and what word combinations are best in what situations.

Speech and language disorders can occur in the same person:

Receptive language disorder: difficulties understanding others (receptive language)

Expressive language disorder: difficulties sharing thoughts, ideas, and feelings

Speech disorder: Difficulties to produce speech sounds correctly or fluently, or voice problems.

Receptive language delay: difficulties understanding the meaning of gestures, following directions, answering questions, identifying objects and pictures and taking turns when talking with others.

Expressive language delay: difficulties with asking questions, naming objects, using gestures, putting words together into sentences, learning songs and rhymes, using correct pronouns or knowing how to start a conversation and keep it going.

Childhood apraxia of speech (CAS): a motor speech disorder characterized by difficulties saying sounds, syllables, and words. The individual knows what he or she wants to say, but the brain has difficulty coordinating the muscle movements necessary to say those words.

Dysarthria: a motor speech disorder caused by impaired movement of the muscles used for speech production, including the lips, tongue, vocal folds, and/or diaphragm. The type and severity of dysarthria depend on which area of the nervous system is affected.

Speech sound disorder: difficulties with articulation (making sounds) and phonological processes (sound patterns) leading to reduced intelligibility (degree to which speech can be understood).

Language-based learning disabilities: problems with age-appropriate reading, spelling, and/or writing which can occur in children with normal intelligence and in children with intellectual disability. For example dyslexia.

Selective mutism: a child who does not speak in certain situations such as at school. The child speaks at other times, such as at home or with friends.