Family aggregation of Language Impairment in an Isolated Chilean Population from the Robinson Crusoe Island

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Abstract

Background: It has been reported that the inhabitants of the Chilean Robinson Crusoe Island have an increased frequency of Specific Language Impairment (SLI) or Developmental Language Disorder (DLD). **Aims:** In this paper, we aim to explore the familial aggregation of DLD in this community. **Methods & procedures:** We assessed the frequency of DLD amongst colonial children between the ages of 3 years and 8 years, 11 months (50 individuals from 45 nuclear families). Familial aggregation rates of language-disorder were calculated by assessing all available first-degree relatives (n= 107, 77 parents, 25 siblings, 5 half-siblings) of the probands. **Outcomes & results:** We found that 71% of the child population performed significantly below expected in measures of phonological production or expressive and receptive morphology. The majority of these children presented with severe expressive and/or receptive language difficulties. A quarter of language disordered probands primarily had phonological difficulties. Family members of affected probands, experienced a higher risk of language-disorder than those of typically-developing probands. This increased risk was apparent regardless of nonverbal IQ. **Conclusions & implications:** Our study substantiates the existence of a familial form of speech and language disorder on the Robinson Crusoe Island. Furthermore, we find that the familiality is stable regardless of non-verbal IQ, supporting the recent movement to reduce the importance of nonverbal IQ criterion in DLD diagnoses.

What this paper adds

It has previously been reported that the Robinson Crusoe Island in Chile experiences an increased risk of language disorders and that this may be due to shared genetic effects within this small isolated population. The investigation of familial clustering patterns can provide support for the involvement of genetic factors and can shed light upon overlaps between different traits. This study demonstrates significant familial clustering of language disorder in the Robinson Crusoe population supporting the role of genetic factors. We further find that the aggregation rates are consistent irrespective of nonverbal ability. These findings suggest that the critical area of impairment in the Robinson Crusoe population is language-based. Our study further suggests that genetic contributions may be shared across neurodevelopmental disorders and that cognitive referencing does not necessarily distinguish between subsets of language-impaired individuals supporting the recent movement to abolish the nonverbal IQ criterion in language disorder diagnoses.

INTRODUCTION

The consideration of family history and heritability data form the basis of the identification of genetic risk factors for complex disorders. Disorders of genetic origin often occur at increased frequencies in small, isolated populations of recent origin (so-called Founder populations) (Bodmer and Cavalli-Sforza, 1976, Hamamy et al., 2011). This is accounted for by the reduced genetic variability and increased rates of consanguinity found in such populations. One Founder population that is of particular interest in the study of language is the Robinson Crusoe Island in Chile (Villanueva et al., 2008).

The Robinson Crusoe Island, together with Santa Clara, Alejandro Selkirk and a set of small islands, form the Juan Fernandez Archipelago, 667km to the West of mainland Chile. Robinson Crusoe is the only inhabited island in the Archipelago and was last colonized by 64 individuals in 1876. According to the CENSUS 2002 (Chilean National Institute of Statistics), the Island houses 633 inhabitants. This figure includes both colonizer families (i.e. individuals directly related to the members of the Founder party in 1876) and immigrant families (i.e. families who have moved to the Island since the last colonization and are not related to the Founder party). All inhabitants of the Island (colonizer and immigrant) live in a single town and speak typical Chilean Spanish. All children attend a single school which follows the curriculum of Continental Chile with the same grading system. Contact with the mainland has historically been limited but the Island is now served by a regular plane service during the summer months and a monthly boat in winter. Children often travel to the mainland for dental and medical treatment and must relocate to the mainland if they wish to go onto Higher Education. The main employment opportunities arise from fishing (lobster

export forms the main income of the Island) and hospitality (the Island receives approximately 100 tourists per year).

A previous investigation of the Robinson Crusoe population found that 35% of colonizer children are affected by Specific Language Impairment (SLI) (Villanueva et al., 2008). In contrast, the rate of language impairment in immigrant children co-incided with that expected for mainland Chile (3.8%) (Villanueva et al., 2008). Furthermore, 85% of children with language-impairment were found to be related to a single Founder family. It is therefore proposed that the increased incidence of language disorder in this population represents a strong genetic effect that has been exacerbated by geographical isolation. (Villanueva et al., 2011, Villanueva et al., 2015, Villanueva et al., 2010). Indeed, recent investigations have identified chromosome regions (on chromosomes 7 and 16) and specific genetic variations (in the *NFXL1* gene) that co-segregate with language disorder in this population (Villanueva et al., 2015). Critically, however, these genetic studies are all based upon the observation that children with language-impairment are descended from a single Founder family (Villanueva et al., 2008). To date, no study has explicitly investigated the patterns of language traits within immediate family members. Such studies are crucial to establish the importance of familial factors and will substantiate the theory of genetic contributions.

Many other studies have verified the importance of genetic factors in the aetiology of neurodevelopmental disorders and speech and language impairments within other populations (Stromswold, 1998, Tomblin and Buckwalter, 1998, Conti-Ramsden et al., 2007, Tallal et al., 2001, Flax et al., 2003). Stromswold reported that across family studies, between 24 and 78% of the SLI proband groups reported a positive family history of

language problems. This compared with between 3 and 46% of the control group (Stromswold, 1998). The prevalence of language disorder is estimated at ~7.6% in British children at school entry (Norbury et al., 2016) and at ~4% in mainland Chile (where it is labelled as Trastorno Específico de Lenguaje (TEL)) (De Barbieri et al., 1999). The familial clustering of language disorders has been shown to be consistent across alternative study designs (retrospective/prospective) (Choudhury and Benasich, 2003) and language assessment schedules (Tallal et al., 2001) but these studies have primarily been performed in populations from developed countries. It is consistently reported that nuclear relatives of language-impaired probands are also at an increased risk of reading difficulties and academic failure than family members of control individuals (Tallal et al., 1989, Barry et al., 2007, Flax et al., 2003, Kalnak et al., 2012). In general, heritability is higher in individuals with mixed expressive- and receptive-impairments, as well as in males (Choudhury and Benasich, 2003, Conti-Ramsden et al., 2007, Hayiou-Thomas, 2008). The findings of these family studies are corroborated by data from twin-pair samples (Bishop et al., 1995, Lewis and Thompson, 1992, Tomblin and Buckwalter, 1998, Hayiou-Thomas, 2008, Hayiou-Thomas et al., 2005, Bishop et al., 2006) and indicate a complex model of inheritance within which the risk of language disorder depends upon multifaceted interactions between numerous genes and environmental factors (SLIC, 2002).

Complexities regarding the deficit(s) underlying language impairment and the relationships between language and comorbid neurodevelopmental disorders have led many to question the utility of the term SLI (Leonard, 2014, Mueller and Tomblin, 2012). The nonverbal criterion associated with this diagnosis was felt to exclude many children from clinical services. A lack of gold standard diagnostic tests led to variability in diagnostic labels and a

general lack of recognition (Ebbels, 2014, Bishop, 2010). In reflection of these issues, the diagnostic term SLI was integrated into the "speech and language disorders" category of the DSM-5 (American-Psychiatric-Association, 2013). A recent Delphi exercise, involving professional stakeholders from the UK, USA, New Zealand, Ireland, Canada and Australia, recommended the use of the term "Developmental Language Disorders (DLD)" over SLI. This terminology has been endorsed by the Royal College of Speech and Language Therapists in the UK (Bishop et al., 2017, Bishop et al., 2016).

The DLD classification is appropriate for all children with language difficulties that impact their everyday life, persist beyond the age of five years and are not associated with a differentiating medical condition such as brain injury, neurodegeneration, a genetic syndrome, Autism Spectrum Disorder or intellectual disability. As such, the term allows for the presence of risk factors (neurobiological or environmental), comorbid neurodevelopmental disorders (e.g. ADHD, Developmental Co-ordination Disorder, verbal dyspraxia and dyslexia) and nonverbal deficits not sufficient to warrant a diagnosis of intellectual disability (Bishop et al., 2017). The DLD label can be accompanied by a specification of the nature of the language impairment (e.g. phonology (in the case of Speech-Sound Disorder (SSD)), grammar, semantics, word finding, pragmatics or verbal learning and memory) but, in general, the use of specific "subtypes" is not recommended.

A nested diagnostic approach has yet to be widely applied in Chile where there are established and defined guidelines regarding the diagnosis of TEL across educational, medical and municipal levels. Across Chile, all children are screened at school entry for language difficulties using tests of phonological ability, expressive and receptive morphosyntax and nonverbal intelligence using the standard tests employed in this study.

Children who perform more than 2 Standard Deviations (SD) below expected across these tests are flagged for additional language support within the school system.

In this study, we sought to document the familial aggregation patterns of language impairment in the colonizer families resident on the Robinson Crusoe Island. This information was used to validate the theory of genetic aetiology in this population. Given the recent move to accept comorbid nonverbal deficits in the diagnosis of DLD, we further used the aggregation data to explore the familial relationships between language and nonverbal IQ. This investigation provides additional insights into the language deficits within this particular population and sheds light upon overlaps between different cognitive traits.

MATERIALS & METHODS

Study Design and Cohort Selection

In this study, all families were ascertained on the basis of a single child (the proband). Probands were defined as age-appropriate (between the ages of 3 years and 8 years, 11 months) colonial children (i.e. children who were directly related to one or more member of the Island Founder party in 1876) who inhabit the Robinson Crusoe Island and regularly attend school. Our study included the entire colonizer population; a total of 59 children from 50 families. Note that this sample set includes the children previously described in Villanueva et al 2008 (Villanueva et al., 2008), in addition to 22 children assessed at a later date (Summer 2009).

All children were assessed using standard language and IQ measures as detailed below. In some families more than one child was aged between 3 and 9 years resulting in non-independence. In these cases, we therefore selected the oldest child as the “proband” and the younger children were treated as siblings. This adjustment left 50 probands from 50

families. On the basis of our assessments, probands were classified as “language-impaired” or “typically-developing” as described below. The language abilities of all available immediate family members of the probands were also assessed allowing the comparison of familial impairment rates between language-impaired and typically-developing proband groups.

The investigation design and contents were described to all subjects prior to participation and all participants gave informed consent. The purpose and data collection methods were approved by the Ethics Board of the School of Medicine, University of Chile and the local authority of the Robinson Crusoe Island.

Proband Assessment

In this study, we employed standard regulation tests and diagnostic thresholds as mandated by the Ministry of Education in Chile (MINEDUC, "Supreme Decree No. 1300") (Ministry of Education of the Government of Chile, 2002). This law decrees that the Chilean educational system must make adjustments for individual with special needs and sets out guidelines for the diagnosis of language disability. These standard tests and thresholds are employed for the diagnosis of language impairment by all educational facilities throughout Chile and were all designed and normed within Chile with the specific aim of diagnosing language disorder. They all have available validity and reliability data. Thus it should be noted that although the diagnostic criteria employed in this study differ from those applied in the UK or USA, the children identified as language impaired in this study would also be diagnosed as having SLI in a study in mainland Chile.

The child assessment battery measured phonology, expressive and receptive morphosyntax and nonverbal intelligence. In addition to these psychometric tests, a parental interview,

medical history data, auditory screening and an oral motor clinical assessment (Villanueva, 2000) were collected for all children aged below 9 years. The oromotor assessment involves a clinical examination for signs of craniofacial malformations, dentomaxillary abnormalities or neuromuscular alteration. Examination is followed by a task in which children must imitate mouth shapes, sounds and movements made by the examiner. This test allowed the exclusion of neuromuscular medical conditions or oromotor dyspraxia – a clinical phenotype that has previously been associated with mutations in the *FOXP2* gene (Morgan et al., 2016). All tests were administered in a school-setting by native Chilean-Spanish-speaking researchers who are professionally trained speech and language pathologists. All tests included training items in which the child's understanding of the task was confirmed.

Phonological production was evaluated using TEPROSIF-R (Maggiolo and Pavez, 2000, Pavez et al., 2008a), the only phonological instrument created and normed in Chile. This test includes 37 single-word items in which the child has to imitate a deferred phonological representation. The target word is first provided by the tester and supported by an image of the required item. For example, the examiner might say "Look, here is a duck" (while showing a picture of a duck). The examiner would then point to a picture of a duck on the water and say "In the water is a…"and the child is expected to complete the sentence using the stimulus word "duck". The items are selected for their phonological characteristics and syllabic complexity. The response is scored in relation to the quantity, type and frequency of phonological simplification processes used by the child rather than their ability to accurately name the picture. All responses were phonetically transcribed and scored post-test. Since this is a diagnostic schedule, the total number of phonological simplifications is transformed into a three-tiered classification; "typical" (error rate no more than 1SD above expected for

age), “at risk” (error rate 1-2SD above expected for age) or “impaired” (error rate more than 2SD above expected for age) (Pavez et al., 2008b). These classifications correspond to the white, dark grey and black shading respectively in Figure 2. In Chile, children considered to be at risk would be referred for additional assessment. Children who meet the criteria for impaired phonological production would be directly referred for additional educational support. Expected error rates were derived from a sample of 620 typically developing children (322 male, 298 female), aged 3-6;11 across different regions of Chile representing different socioeconomic levels (based on vocational level of parents). In this sample, it was found that typically developing children aged above 7 perform at ceiling level (Pavez et al., 2008b). Evaluation of 44 children (30 male, 14 female) with language disorder and 44 age- and gender-matched controls, indicated that TEPROSIF-R is sensitive to the identification of language disorder (language-impaired children had an average error rate of 26.3±13.9 while children with typical language development had an average error rate of 10.8±8.7) (Pavez et al., 2008b). The test has a high internal consistency with a Cronbach Alpha coefficient of 0.90 (Pavez et al., 2008a). The errors documented in this study matched those expected and detailed in the normalization sample, indicating that the Island children did not have a strong regional dialect.

Expressive and receptive morphosyntax were examined with a Chilean Spanish adaptation of the Toronto Spanish Grammar Exploratory test (TEGE or STSG) (Pavez, 2003). Again, this test is the only morphosyntactical instrument created in Chile. The test consists of an expressive and receptive scale and each scale consists of 23 items. In the expressive component, children must repeat sentences of increasing length and complexity in terms of grammatical structure. In the comprehensive component, children must use

morphosyntactic cues (e.g. verbs, gender, tense, passive/active) to identify the picture that matches a target sentence from a choice of four pictures (Pavez, 2003). On the basis of their performance, children are classified as "typical" (above 25th percentile), "at risk" (between 10th and 25th percentile) or "impaired" (below 10th percentile) for each subtest (Pavez, 2003). These classifications directly relate to the white, dark grey and black shading respectively in Figure 2. In Chile, children designated as "at risk" would be referred for further assessment and/or monitoring. Children diagnosed as "impaired" would be directly referred for additional educational support.

Chilean validation and normalization data were generated from 120 typically developing Chilean children (60 male, 60 female) (aged 3-7 years) (Pavez, 2003). Evaluation of 30 children (15 male, 15 female) with language disorder and 30 age- and gender-matched controls, indicated that TEGE is sensitive to the identification of language disorder (Pavez, 2003). Both components have a high inter-item reliability with test/retest correlations of 0.77 for the expressive component and 0.83 for the receptive component (Pavez, 2003).

Nonverbal intelligence was assessed with the Columbia Mental Maturity Scale which provides a measure of reasoning ability in children aged 3 years 6 months to 9 years 11 months. The test consists of 51-65 elements, each of which includes a series of 3 to 5 drawings from which the child must identify the odd one out (Burgemeister et al., 1998a, Burgemeister et al., 1979). This is the standard child intelligence test in Chile. It has a test-retest reliability of 0.85 and shows high correlation with the Raven's colour matrices (Burgemeister et al., 1979, Burgemeister et al., 1998b).

Proband Classification

On the basis of the above measures, probands were designated as having a Developmental Language Disorder (DLD group) or having Typical Language Development (TLD group) as defined below.

DLD group – In order to be classified as having DLD, children had to be perform below expected levels in at least one of the language tests performed. Thresholds were defined as performance more than 2SD below expected (for children aged 6 years or less) or performance >2 years below expected for their chronological age (for children aged over 6 years who are expected to make zero errors) on the TEPROSIF-R and below the 10th percentile on either the receptive or expressive scales of the TEGE (i.e. recommended thresholds for Chilean children in the tested age range). For later exploratory stages, the nonverbal IQ data from the Colombia test was used to further sub-divide the DLD group - those with IQ below the 10^{th} percentile and those with nonverbal IQ above this threshold. All scores were collated as raw scores and compared against normative Chilean samples of a similar age (Pavez, 2003, Pavez et al., 2008b). These diagnostic thresholds match the national Chilean standards, as decreed by the Ministry of Education in Chile (MINEDUC).

TLD group – In order to be classified as having typical development, children had to perform within the typical range on all tests of morphosyntax (performance not more than 2SD below expected (for children aged 6 years or less) or performance not more than 2 years below expected for their chronological age (for children aged over 6 years) on TEPROSIF-R), phonology (performance above the 10th percentile on both the receptive and expressive scales of the TEGE) and nonverbal IQ (Columbia Intelligence score above the 10^{th} percentile).

Exclusions – Any proband who presented with typical language but IQ below the tenth percentile (n=5) were excluded from the study as they did not meet criteria for typical development. The final sample size therefore consisted of 45 probands from 45 families.

Family Assessment

We sought to record the familial aggregation of language difficulties in the immediate family members of all 45 probands by the assessment of all available first-degree relatives (n= 124, 82 parents, 30 siblings, 12 half-siblings).

The majority of these family members (n=115) were aged above 9 years of age and therefore outside of the normative age for available Chilean tests. For these individuals, we therefore used standardized Spanish assessments. These included tests of verbal fluency and comprehension and nonverbal IQ as described below. Testing was carried out according to standard administration for each test. All tests were administered in a school-setting by native Chilean-Spanish-speaking researchers who were professionally trained speech and language pathologists. All tests included training items in which the individual's understanding of the task was confirmed. In addition to direct assessment, all family members completed the family history inventory (kindly provided by P Tallal) (Tallal et al., 2001). This survey consists of a range of questions concerning early development, medical history and language and learning difficulties in family members, allowing the identification of possible past language and/or learning impairments as well providing an index of family history of language, reading or writing deficits.

Verbal fluency was measured using two verbal elicitation tasks from the Barcelona test; one semantic and one phonological (Singh, 2011). In the first, individuals are asked to name as many animals as they can think of in one minute. In the second, they are asked to name as

many words beginning with the letter 'p' as they can think of. Items are scored as the number of responses that meet each category. The test-retest validity of the Barcelona test is high (0.92) as is the inter-item reliability (0.99) in typical subjects (Singh, 2011).

Verbal comprehension was assessed using the Token test (De Renzi and Vignolo, 1962) in which subjects are asked to point to series of shapes. Each series increases in complexity and shape number as the task progresses. This task consists of 36 items and has a high internal reliability (0.92).

Nonverbal ability was assessed using the Raven progressive matrices (Raven et al., 2003) in which the subject must complete a series by selecting the appropriate geometric design. The Raven test is a measure of fluid intelligence that includes 60 items and has a high reliability (0.81-0.87).

Classification of Family Members

In accordance with the probands, all family members were classified as having "typical language" or "language disorder" as defined below:

Language disorder – Family members who performed below the 10th percentile on either the Barcelona (verbal fluency) test or the Token (receptive comprehension) test and self-reported a need for writing or reading support at school or a history of speech and language impairment (unless noted to be just stuttering) in the family history questionnaire were classified as having "language disorder". This term acknowledges the fact that no developmental data were available for these individuals and that the diagnostic sensitivity may differ between probands and family members, given the lack of available measures of syntactic expression for adults and older children. For later, exploratory stages, the nonverbal IQ data from the Ravens matrices was used to further divide this group into those

affected by language difficulties with nonverbal IQ below the 10th percentile and those with language difficulties and typical nonverbal IQ.

Typical Language – Family members were classified as having "typical language" if they performed above the 10th percentile on both the Barcelona and Token tests and self-reported no need for writing or reading support at school and no history of speech and language impairment (unless noted to be just stuttering) in the family history questionnaire.

Exclusions – In total, 124 family members were assessed. Direct IQ data were not available for 16 family members and for one individual, no language data were available. These individuals were therefore excluded from the cohort leaving 107 family members (77 parents, 25 siblings, 5 half-siblings) for analysis.

Relative risks and their confidence intervals and significance were calculated using MEDCALC (https://www.medcalc.org/calc/relative_risk.php). P-values were derived from the z-statistic.

RESULTS

Our investigation of 45 (22M:23F) independent colonizing Island inhabitants aged between 3 years, 4 months and 8 years, 11 months yielded a total frequency of DLD of 71.1% (Figure 1).

<Figure 1 about here>

The language difficulties observed in probands were variable between individuals, supporting the complexity of aetiology, even within this closely-related population (Figure 2). Half of the DLD probands presented with mixed receptive-expressive difficulties (Figure 2). Probands with nonverbal deficits tended to show more severe and widespread deficits

across all three tasks than children without nonverbal deficits (Figure 2). Only one proband had isolated expressive problems, while three probands showed deficits only on the receptive TEGE. Eight children primarily had difficulties with the phonological task and may have received a differential diagnosis of Speech Sound Disorder (SSD) in other settings. Note however that all of these children also performed below average on tests of expressive or receptive language (Figure 2) and were aged above 6 years indicating that their difficulties extended beyond speech production and were persistent in nature, warranting a diagnosis of DLD (Bishop et al., 2017).

<Figure 2 about here>

As a group, DLD-probands performed 11 months below age expected on the task of phonological production (TEPROSIF-R), 25 months below expected on tests of receptive morphology and 22 months on tests of expressive morphology (Table 1). Many TLD probands were also found to perform marginally below age-expected on the receptive TEGE task, although, by definition, this was not to a level that warranted a DLD diagnosis (Figure 2, Table 1). No evidence of oromotor dysfunction was observed in any of the DLD probands.

<Table 1 about here>

We investigated all available first-degree relatives (parents, siblings and half siblings) of these 45 probands (107 individuals from 45 families). These individuals had an average age of 31 years, 5 months and included 77 parents, 25 siblings and 5 half-siblings (Table 2). Across all family members assessed, 45.8% showed evidence of language disorder (Figure 1).

<Table 2 about here>

In order to explore the patterns of aggregation of language disorder, we began by comparing the frequency of family member language difficulties across the two proband

groups (DLD vs TLD) (Figures 1 and 2). We found that the rate of language difficulties was significantly higher among family members of DLD probands; 53.8% of family members of DLD probands experienced language difficulties compared to 24.1% of family members of TLD probands (Figure 1). These frequencies yield a relative risk ratio of 2.2 (95% CI 1.13-4.39, P=0.02) for family members of DLD probands against family members of TLD probands (Table 3). We did not observe any obvious clustering of the types of difficulties found in family units (Figure 2).

Of the total DLD proband group, half presented with nonverbal deficits (Figure 1). The non-verbal IQ of the DLD probands, as a group, was 2 years, 3 months below age-expected. In order to explore the role of nonverbal IQ in language impairment, we therefore further classified DLD probands as having DLD with typical nonverbal IQ or DLD accompanied by low nonverbal IQ. The rate of language disorder in family members was consistent across these two subgroups; 54.8% of family members of DLD probands with typical nonverbal IQ presented with language disorder compared to 52.8% of family members of DLD probands with low nonverbal IQ (Figure 1). Similarly, the rates of nonverbal difficulties were comparable in family members; 21% of family members of DLD probands presented with language disorder accompanied by typical nonverbal IQ (relative risk of 2.97), and 33% presented with language disorder accompanied by low nonverbal IQ (relative risk of 1.93) (Figure 1).

Interestingly, when we split family members according to their relationship to the proband (parents or siblings/half-siblings), we observed that the aggregation of language disorder was stronger between parents and probands than between siblings and probands (Table 3). Parents of DLD probands were more likely to have language disorder than parents of TLD

probands (56.7% vs 16.7%, Relative risk 3.4, P=0.0096). This effect was consistent across both Fathers and Mothers (Table 3). In contrast, siblings of DLD probands showed no such increase in risk (45% vs 60%, Relative risk 0.8) (Table 3). However, it should be noted that there are a small number of siblings available in the TLD proband group (n=5).

<Table 3 about here>

Lastly, we investigated the effects of gender upon risks of language-impairment. Half of the DLD probands were male and across all 45 probands, the rate of DLD was 72.7% in males and 69.6% in females. Among the 49 family members who presented with language disorder, 20 (40.8%) were male and 29 (59.2%) female. Across all 107 family members, 41.7% of males and 49.2% of females tested had language disorder. The relative risk of Fathers of DLD probands was found to be marginally higher than that of Mothers of DLD proands, although this did not reach significance (Table 3). Family members of male DLD probands had a higher risk of DLD than family members of female DLD probands (relative risks of 3.1 and 1.6 respectively) (Table 3).

In summary, among the Robinson Crusoe population, we found consistent evidence for a specific familial aggregation of DLD, regardless of nonverbal IQ. In particular, we found that family members of male DLD probands showed an increased risk of language disorder.

DISCUSSION

It has previously been reported that the child inhabitants of the Robinson Crusoe Island have a frequency of speech and language impairments that is higher than that observed in mainland Chile. Although assumed to be genetic in nature, the familiality of these impairments has yet to be substantiated. In this paper, we confirm the increased frequency

of DLD in an extended child population. We go on to demonstrate familial aggregation of language difficulties within this population.

In our investigation, we found that 71% of the child population and 46% of adults were affected by language disorder. This risk is significantly inflated above that reported in mainland Chilean populations despite the use of reliable Chilean measures and standard diagnosis thresholds. While this may indicate that the tests employed are not valid for this particular population, it should be noted that all tests were administered by speech and language pathologists who regularly use the measures within mainland populations. The researchers report that the Island children understood what was expected of them, completed the training items in the way expected and did not have any linguistic peculiarities that can explain the high diagnosis rate. An item-by-item comparison of responses given by Islanders and mainland children on the phonological task indicated that the errors did not represent a regional dialect. Furthermore, it should be noted that some children did reach age-expected levels on the tasks administered and that many children on the Island are within their expected grade levels at school. Since the school follows a mainland curriculum and examination system, this indicates that most children are performing at expected levels within an educational setting.

An alternative explanation for the observed level of DLD may be the presence of genetic and/or environmental risk factors on the Island. A previous study found that the rate of SLI in immigrant Island children co-incided with the expected level on mainland Chile (3.8%) (De Barbieri et al., 1999), indicating that environmental factors do not account for the high frequency of language impairment. The authors concluded that, given the population history, the most likely alternative source of risk would be shared genetic factors (Villanueva

et al., 2008). Our study supports this hypothesis. Although our TLD probands were selected to be unrelated to DLD probands in terms of nuclear family (Father, Mother and siblings), it is likely that they share common recent ancestors (Grandparents or Aunts and Uncles) since the entire population is derived from only 64 individuals over 5 generations. This observation may account for the relatively high level of language disorder seen in family members of TLD probands. Since genetic contributions to language impairment are expected to be complex in nature, it is possible for unaffected individuals to carry a relatively high burden of risk variants without themselves being affected (Newbury and Monaco, 2010).

The language deficits we observed were highly heterogeneous between individuals and families, and represented the patterns typically seen in language-disordered populations. The difficulties documented in this study support the use of the label "DLD" to describe the difficulties experienced by Robinson Crusoe inhabitants. This further directs their clinical care as it indicates they would benefit from the same system of diagnosis and therapy as given to mainland children.

Previous studies have highlighted the importance of *FOXP2* mutations in inherited speech and language disorders (Lai et al., 2001, Morgan et al., 2016). In this investigation, we did not observe any evidence of oromotor dyspraxia – the core clinical phenotype associated with *FOXP2*-related speech and language disorders (Morgan et al., 2016). Although we cannot rule out *FOXP2* involvement from language behavior, this observation supports the findings of genetic sequencing studies which suggest that *FOXP2* is not involved in the language disorder found on Robinson Crusoe (Villanueva et al., 2015).

The influence of genetic risk factors are supported by the familial aggregation of language disorders within family units; family members of DLD probands had a relative risk of 2.23 when compared to family members of TLD probands, a figure that is in line with that previously reported (Stromswold, 1998). This observation appeared independent of nonverbal IQ in the DLD probands, half of whom presented with low nonverbal IQ (Figure 1). Although the diagnosis of SLI traditionally requires a normal nonverbal IQ, recent studies suggest that children with DLD do score below their peers on tests of nonverbal ability (Gallinat and Spaulding, 2014, Miller and Gilbert, 2008, Botting, 2005). The observations of extensive comorbidity (Bishop and Snowling, 2004, Rutter, 2008) and familial clustering of broad phenotypes of language and learning difficulties (Landerl and Moll, 2010, Barry et al., 2007) further suggest that contributions may be shared across neurodevelopmental disorders (Tomblin and Mueller, 2012). In terms of the impairments seen in the family members, we again found that nonverbal IQ did not distinguish between subgroups. Nonverbal IQ did not provide a marker of familaility; language-disordered family members of DLD probands presented with both typical nonverbal IQ and DLD with low nonverbal IQ (Figures 1 and 2). These findings again suggest that cognitive referencing does not necessarily distinguish between subsets of language-disordered individuals (Norbury et al., 2016) and, furthermore, indicates that the critical area of impairment in the Robinson Crusoe population centres around language rather than learning, further directing their clinical care and providing information for family members.

Previous studies have shown that the heritability of language disorder increases in severely disordered subsets of children (Viding et al., 2004, Choudhury and Benasich, 2003). It is hypothesized that a supportive learning environment can overcome inherent language

difficulties in less severely affected children while this is not the case for more severely affected children (Steen, 2010). Recent studies have questioned whether nonverbal ability should be considered in the diagnosis of language impairments at a clinical level (Bishop, 1994, Bishop, 2014, Reilly et al., 2014, Norbury et al., 2016). Our study of this small population indicates that language disorder shows familial clustering regardless of intellectual ability supporting the argument to abolish the nonverbal IQ criterion in language disorder diagnoses.

It is often reported that language impairment affects a higher number of males than females (Shriberg et al., 1999). In our study, we found little evidence for a gender-specific effect. In terms of relative risk, Fathers of DLD probands, and family members of male DLD probands had a higher risk than Mothers or family members of female DLD probands (Table 3). These trends reflect those reported in a previous study of familial patterns of SLI (Conti-Ramsden et al., 2007) and support the presence of a female protective mechanism by which females with IQ in the normal range can withstand a greater risk burden than males (Robinson et al., 2013). The size of our sample prohibits further decomposition of the proband group by IQ but we note that all the probands presenting with low IQ and normal language (5 individuals) were female (Table 2) further supporting this argument.

Limitations

The focus of this study was upon a small population who live in an isolated location with unique social and geographical pressures. It is these circumstances which make this population so interesting. However, the same conditions place unavoidable limitations on a study of this nature.

The use of standardized South American test procedures and the existence of a consistent school syllabus allow a direct comparison with prevalence rates in Continental Chile. Nonetheless, the availability of standard and normalized Chilean tests limited comparisons with studies outside South America, where language domains such as semantics are generally considered and different diagnostic tests employed. Similarly, the availability of standardized tests necessitated the use of different tasks for child and adult participants. All probands were selected to fall within the range of standard child tests making the proband diagnosis consistent but there may be some disparity in the exact language domains measured between adult family members and child probands. In addition, this study provides a snapshot of the difficulties experienced by language-impaired children on the Island. A more detailed picture of individual difficulties would require the addition of extra tests within a longitudinal study design.

While we have labelled our tests by the domains that they aim to capture, as with all psychometric tests, poor performance may be observed for many reasons. For example, problems with expressive morphosyntax may be driven by memory limitations or vocabulary difficulties.

Our previous findings indicate that, despite differences in diagnostic schedules, the genetic contributions to language disorder in this population do overlap with those found in European populations – rare variants in the *NFXL1* gene were associated with DLD in the Robinson Crusoe population and replicated in the European SLIC cohort (Villanueva et al 2015). These findings indicate that the major mechanisms contributing to DLD may be preserved across populations, even if the diagnostic criteria differ.

SUMMARY

In summary, our study supports the existence of an increased rate of DLD on the Robinson Crusoe Island and indicates that the presenting language disorder is familial in nature supporting the role of genetic factors. Furthermore, we demonstrate that the core phenotype in this population is language-related rather than cognitive in nature.

BIOETHICS COMMENT

The investigation design and contents were described to all subjects prior to participation and all participants gave informed consent.

The purposes and data collection methods were approved by the Ethics Committee of the University of Chile Faculty of Medicine (Medical Faculty-University of Chile-Ethics Board) as a part of the projects DID TNAC 01-02/01 and DID MULT 05/05-2 which are financed by University of Chile. Prior proceeding, the University of Chile signed an agreement with Ilustre Municipalidad de Juan Fernandez.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest.

FIGURE AND TABLE LEGENDS

FIGURE 1 – Flow chart to show study design and frequency of language disorder in proband and family member groups.

Size of each proband group, percentage of final proband set and male to female ratios are shown in boxes. Black boxes represent individuals excluded from the study at each stage.

Frequency of language disorder in all available family members of each proband group is shown as a pie chart for each of the proband groups. In the pie-chart, family members are split according to language status; TL – typical language (regardless of nonverbal IQ), LD – language disorder with typical nonverbal IQ, LD+↓NVIQ – language disorder with low nonverbal IQ.

FIGURE 2 – Heat map of performance across tasks in probands.

Performance across language and nonverbal IQ tests are shown for all probands in the study. Performance significantly below age-expected (-2SD or below 10th percentile) is represented by black shading. Performance 1SD to -2SD below age-expected or between 10th and 25th percentile is shown in dark grey. Performance marginally below age-expected (mean to -1SD or 25th to 50th percentile) is represented by light grey shading. Performance at or above age-expected is represented by white blocks.

TABLE 1 – Raw score statistics and age equivalent scores for all proband groups.

Note that lower score on TEPROSIF denote better performance as this test is scored number of errors.

TABLE 2 – Descriptive statistics of the cohort and subgroups.

50 independent probands between the ages of 3 years, 4 months and 8 years 11 months were tested on measures of language and nonverbal IQ (see methods). Following testing,

the language ability of family members were compared between language-disordered (DLD) and typically-developing (TLD) probands.

a – Probands with typical language and low IQ were excluded from further analyses.

TABLE 3 – Frequency of language disorder among subgroups of family members.

Frequencies are followed by Relative risk and 95% CI (of family members of given proband group compared to family members of TLD probands). Significant ($P<0.05$) relative risks are shown in bold.

FIGURE 1

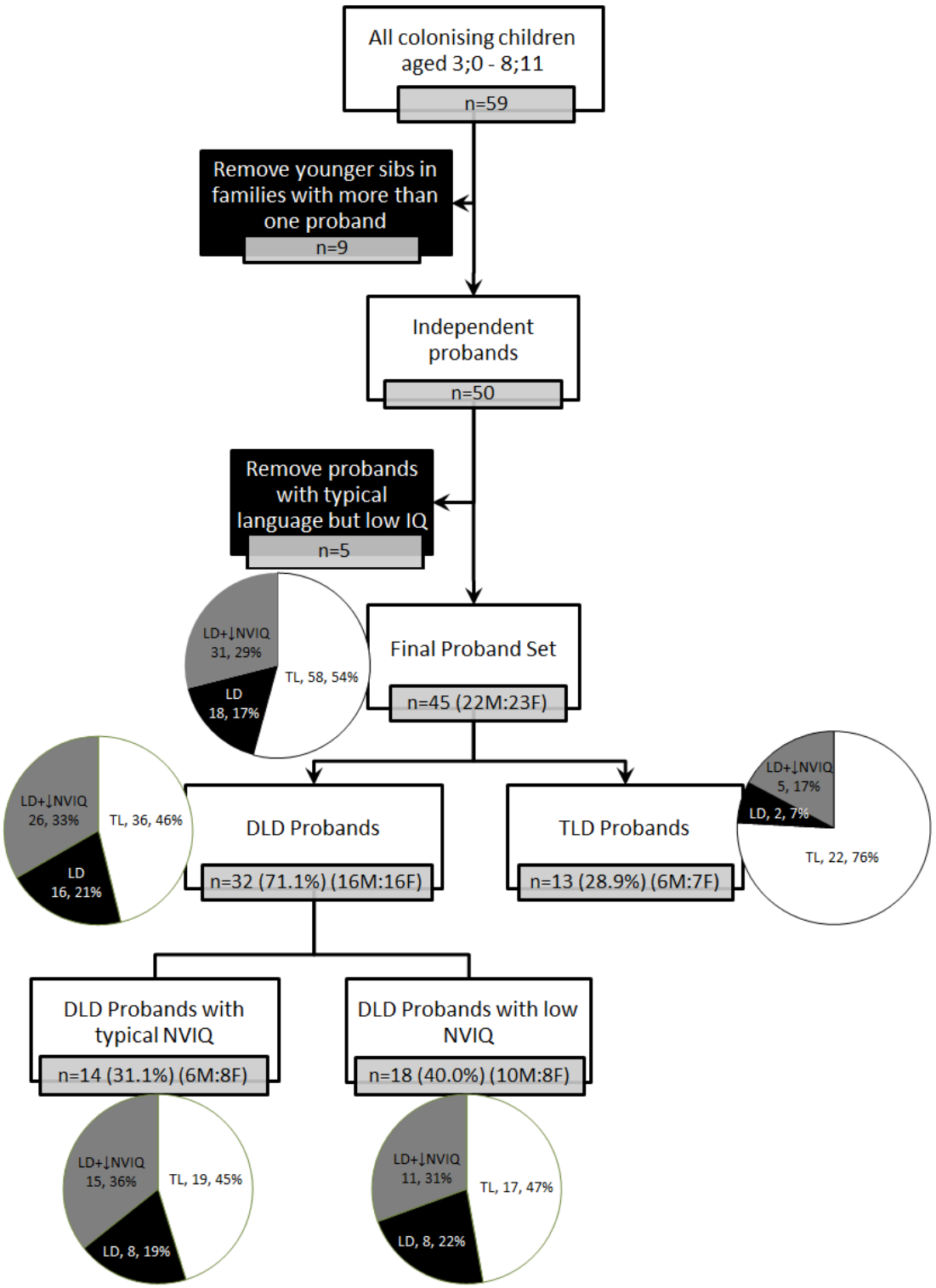
All colonising children aged 3;0 - 8;11
n=59
Remove younger sibs in families with more than one proband
n=9
Independent probands
n=50
Remove probands with typical language but low IQ
n=5
LD+↓NVIQ 31, 29%
LD 18, 17%
TL, 58, 54%
Final Proband Set
n=45 (22M:23F)
LD+↓NVIQ 26, 33%
LD 16, 21%
TL, 36, 46%
DLD Probands
n=32 (71.1%) (16M:16F)
TLD Probands
n=13 (28.9%) (6M:7F)
LD+↓NVIQ 5, 17%
LD, 2, 7%
TL, 22, 76%
DLD Probands with typical NVIQ
n=14 (31.1%) (6M:8F)
DLD Probands with low NVIQ
n=18 (40.0%) (10M:8F)
LD+↓NVIQ 15, 36%
LD, 8, 19%
TL, 19, 45%
LD+↓NVIQ 11, 31%
LD, 8, 22%
TL, 17, 47%

FIGURE 2

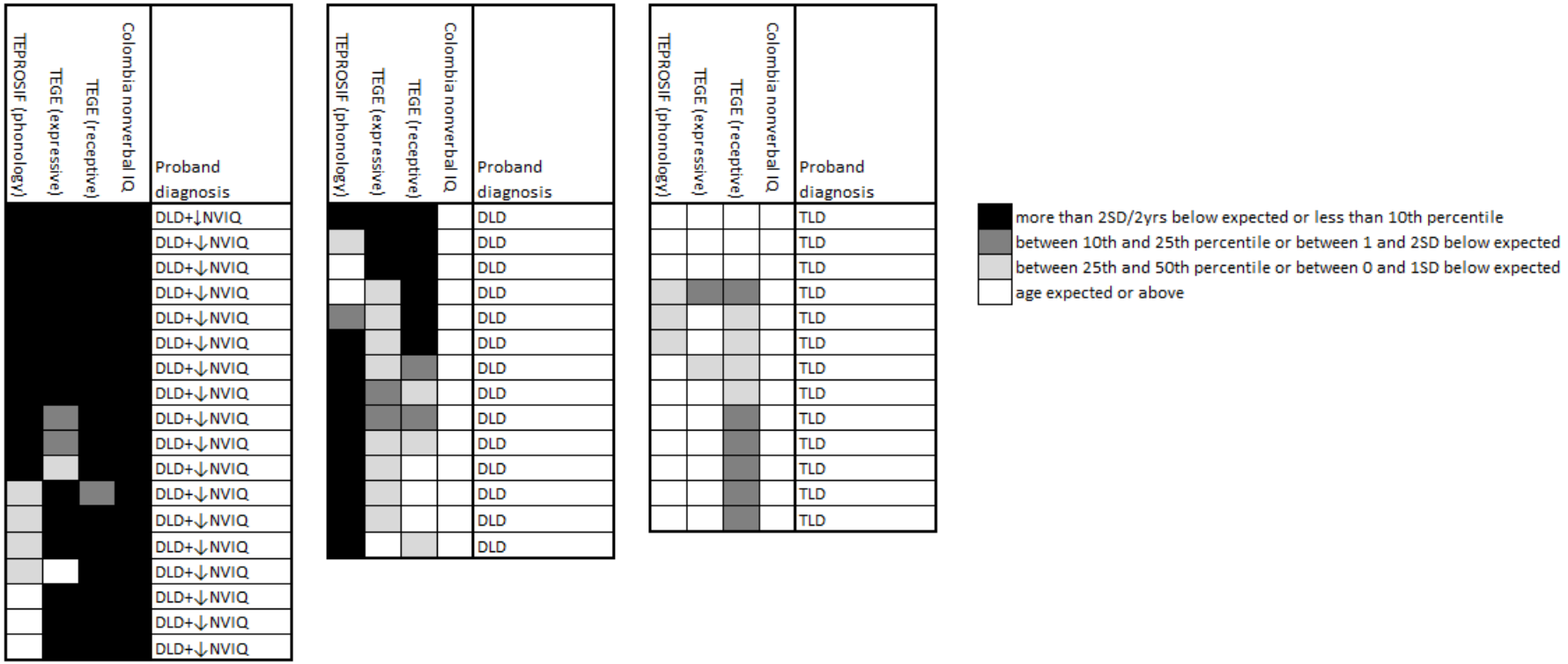
TEPROSIF (phonology)
TEGE (expressive)
TEGE (receptive)
Colombia nonverbal IQ
Proband diagnosis
DLD+↓NVIQ
DLD
TLD
more than 2SD/2yrs below expected or less than 10th percentile
between 10th and 25th percentile or between 1 and 2SD below expected
between 25th and 50th percentile or between 0 and 1SD below expected
age expected or above

TABLE 1

Group	Statistic	TEPROSIF (phonology)	TEGE (comprehension)	TEGE (expression)	COLOMBIA (IQ)
All children (n=59)	Mean	11.34	28.20	24.05	28.76
	Standard Deviation	10.79	11.12	12.79	11.55
	Range	0-49	0-43	0-46	0-46
	Chronological age	5;11	5;11	5;11	5;11
	Performance age	5;7	4;3	4;8	4;2
Non-probands (n=14) (siblings and excluded children)	Mean	6.43	35.07	28.36	27.93
	Standard Deviation	6.02	4.30	11.24	10.96
	Range	0-18	24-41	2-46	0-40
	Actual age	5;11	5;11	5;11	5;11
	Performance age	6;2	4;7	4;11	4;2
DLD probands (n=32)	Mean	14.53	23.56	19.69	24.38
	Standard Deviation	12.50	12.44	12.98	10.75
	Range	0-49	0-42	0-45	0-43
	Actual age	6;2	6;2	6;2	6;2
	Performance age	5;3	4;1	4;4	3;11
TLD probands (n=13)	Mean	8.77	32.23	30.15	40.46
	Standard Deviation	7.56	6.92	10.24	3.95
	Range	0-21	16-43	9-44	33-46
	Actual age	5;3	5;3	5;3	5;3
	Performance age	5;11	4;4	5;3	4;11

TABLE 2

		Count N	Male N (%)	Female N (%)	average age (yrs;mnths)	min age (yrs;mnths)	max age (yrs;mnths)
Before exclusions	All probands tested	50	22 (44%)	28 (56%)	5;11	3;4	8;11
Excluded probands[a]		5	0	5 (100%)	5;11	4;2	8;10
After exclusions	Final proband set	45	22 (49%)	23 (51%)	5;11	3;4	8;11
	DLD Probands	32	16 (50%)	16 (50%)	6;2	3;4	8;11
	TLD probands	13	6 (46%)	7 (54%)	5;3	3;5	7;3
All	parents	77	33 (43%	44 (57%)	37;5	20	56
	siblings	25	13 (52%)	12 (48%)	15;8	4	35
	half siblings	5	2 (40%)	3 (60%)	20;2	14	28
	all	107	48 (45%)	59 (55%)	31;5	4	56
DLD probands	parents	53	22 (42%)	31 (58%)	39;2	26	56
	siblings	20	11 (55%)	9 (45%)	16;4	4	35
	half siblings	5	2 (40%)	3 (60%)	20;2	14	28
	all	78	35 (45%)	43 (55%)	32;0	4	56
TLD probands	parents	24	11 (46%)	13 (54%)	33;6	20	52
	siblings	5	2 (40%)	3 (60%)	12;10	6	16
	half siblings	0	0	0	NA	NA	NA
	all	29	13 (45%)	16 (55%)	29;12	6	52

TABLE 3

	N	TLD probands	DLD probands	Relative risk (95% CI)	P
Family members affected by LD	**107**	**7 of 29 (24.1%)**	**42 of 78 (53.8%)**	**2.23 (1.13-4.39)**	**0.0202**
Parents affected by LD	**77**	**4 of 24 (16.7%)**	**30 of 53 (56.7%)**	**3.40 (1.35-8.57)**	**0.0096**
Siblings & Half-siblings affected by LD	30	3 of 5 (60.0%)	12 of 25 (48.0%)	0.80 (0.35-1.82)	NS
Fathers affected by LD	33	1 of 11 (9.0%)	11 of 22 (50.0%)	5.50 (0.81-37.33)	0.0810
Mothers affected by LD	44	3 of 13 (23.1%)	19 of 31 (61.3%)	2.66 (0.95-7.45)	0.0634
LD family members of male probands	**56**	**3 of 16 (18.9%)**	**23 of 40 (57.5%)**	**3.07 (1.07-8.80)**	**0.0372**
LD family members of female probands	51	4 of 13 (30.8%)	19 of 38 (50.0%)	1.63 (0.68-3.90)	0.2769

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