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Genetics of cleft lip and/or cleft palate: Association with other common anomalies

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ABSTRACT

Cleft lip and/or cleft palate (CL/P) collectively are well known as being amongst the most common birth defects but we still have difficulty explaining why the majority of cases occur. In general, sporadic cases with no family history may be more related to environmental risks, while the presence of one or more affected relative in the same family strongly suggests that genetic factors are the main contributor. Orofacial clefts can occur in conjunction with other defects (syndromic CL/P) or as an isolated defect (non-syndromic – NSCL/P). CL/P syndromes have been studied intensively and appear to have a stronger genetic aetiology. Here we report on the relationship between syndromic and NSCL/P as a phenotypic spectrum resulting from coding or non-coding mutations respectively. We review certain abnormalities that are most frequently associated with CL/P, including dental, heart, brain, skin and certain types of cancer and examine some of the genes that are involved. We include the outcome of recent NSCL/P GWAS data and we will discuss how the genes at these loci might contribute towards clarifying the genetics of CL/P.

1. Introduction

Collectively, orofacial clefts, which include cleft lip with or without cleft palate or cleft palate alone (CL/P), rank among the most prevalent and well known birth defects. The new-born baby with CL/P is likely to have difficulty feeding but will also develop conductive hearing loss, speech problems, dental anomalies and may have associated social and psychological issues. The best patient outcomes benefit from an expert team dedicated to cleft treatment and care including surgical repair, dental and orthodontic work, as well as speech and hearing therapy. Surgery is usually carried out starting from 2 to 6 months but further operations to facilitate improved speech (pharyngoplasty), correct jaw bone growth, orthodontics and cosmetics may all be required at intervals until late teens [Mackay et al., 1999; Stanier and Moore, 2004].

The prevalence of orofacial clefts varies between 1.5 and 25/10,000 births [Mossey and Castilla, 2003]. The average occurrence rate for CL/P is said to be around 1 in 700 new-borns although it is highest in Asia and lowest in Africa [Wyszynsk et al., 1996]. Cleft palate (CP) does not vary significantly with geographical location and has an incidence of 1 in 1500 new-born babies. Most cases of cleft lip (CL) are unilateral (80–85%) [Hagberg et al., 1998] with 33% of those being left-sided clefts [Jensen et al., 1988; Fogh-Andersen, 1942; Fraser and Calnan, 1961; Bonaiti et al., 1982; Tolarova, 1987]. Worldwide, CL/P is more common in males, while CP is more common in females [Fogh-Andersen, 1942; Mossey and Little, 2002; Fogh-Andersen, 1961]. Males with CL/P tend to have a more severe cleft than females [Fogh-Andersen, 1942] and familial CL/P is often less severe than sporadic cases [Fogh-Andersen, 1942; Niswander et al., 1972]. The sex ratio of CL/P in the Caucasian population is 2:1 (male:female) [Mossey and Little, 2002]. However, the predominance in males is lower for syndromic forms defined as where the baby presents with other abnormalities in addition to CL/P) [Mossey and Castilla, 2003]. Curiously, the frequency in females is higher when the father is greater than 40 years [Rittler et al., 2004].

To understand the developmental mechanisms underlying orofacial clefts it is essential to review a large and varied field of research. Causative factors can broadly be grouped into environmental and genetic. Environmental factors that can seriously affect development of the fetus range from maternal age to use of medications such as antiepileptic agents or corticosteroids, smoking and alcohol consumption during pregnancy [Little et al., 2004; Honein et al., 2007]. Maternal illness was suggested to elevate the chance of CL/P [Dietz et al., 2012] while nutritional/metabolic

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problems such as obesity [Stott-Miller et al., 2010], diabetes [Correa et al., 2008] or a lack of dietary folic acid may also be linked [Wilcox et al., 2007]. Genetic factors include aberrant gene variants inherited from the mother or father that may be directly responsible for the cause of CL/P or confer a susceptibility to an increased risk of developing a cleft. Most cases of CL/P are likely to involve a combined effect of environmental and genetic factors during the first weeks of pregnancy. This would also explain why in many families, with multiple affected individuals over several generations, transmission is often through unaffected "carriers". Here the carrier has inherited the same causal variant but escaped the phenotypic consequences, by experiencing a more favourable uterine environment or by co-inheriting a protective genetic background. In other words, the cause of CL/P seems to follow a complex, multifactorial mode of inheritance more often than a strictly Mendelian one, with transmission between generations not being consistently predictable [Mitchell and Risch, 1992; Murray, 2002].

About 50% of patients with cleft lip also have a cleft palate [Stanier and Moore, 2004]. It is thought that this combination most likely represents the result of a mechanical interaction during development. During embryogenesis, the development of the lip precedes formation of the palate. It is thought that if the lip defect is deep enough to affect the primary palate, then the palate cannot close and the cleft palate results as a secondary effect of the CL. In epidemiological terms, these patients are usually included together with CL alone as both are assumed to have a common aetiology. Nevertheless, there are recent data to support the notion that CL and CL/P may also have separate developmental origins [Harville et al., 2005; Genisca et al., 2009; Jugessur et al., 2011]. CP alone is described as an independent defect, since it arises in patients without obvious lip fusion defects. However, to complicate matters, there are also well-documented examples where CL and CP have been found separately in members of the same family [Janku et al., 1980; Kantaputra et al., 2011]. Many studies include data from different types of animal models in order to contribute to the knowledge of CL/P [Gritli-Linde, 2012]. Similar although not identical mechanisms occur in the development of the lip, primary and secondary palates in both mice and chick compared to humans. The use of these models has therefore allowed the research community to more deeply interrogate the molecular mechanisms underlying orofacial clefts [Juriloff and Harris, 2008; Kouskoura et al., 2011], although the species differences still leaves some important gaps in our knowledge.

The classificafion of orofacial clefts with or without other congenital anomalies, as well as chromosomal or gene variations is described in the International Perinatal Database of Typical Oral Clefts [IPDTOC Working Group, 2011] and subsequently modified in 2013 by adding new cleft subgroups [Luijsterburg et al., 2013]. These provide a recommended classification of orofacial clefts into syndromic CL/P and NSCL/P, according to the presence or absence of other congenital anomalies in addition to the cleft. The observed incidence of patients with a cleft and other abnormalities differs between studies and may also vary between populations, but is collectively reported to be approximately 30% [Vallino-Napoli et al., 2006; Beriaghi et al., 2009]. It is also reported that CP is more frequently associated with other congenital anomalies than CL/P [Mossey and Little, 2002]. However, the correlation between specific malformations and types of clefts remains to be fully described or understood [Vallino-Napoli et al., 2006; Beriaghi et al., 2009; Luijsterburg and Vermeij-Keers, 2011; Aqrabawi, 2008].

A great deal of research has focussed on NSCL/P, particularly with the aim to identify the most important genes involved [Murray, 2002; Jugessur and Murray, 2005; Mangold et al., 2009; Marazita et al., 2004; Prescott et al., 2000, Riley et al., 2007b; Vieira et al., 2008b; Mangold et al., 2011]. Many reviews have been published describing the latest progress [e.g. Rahimov et al., 2012; Dixon et al., 2011], even including the prenatal and postnatal prevalence of associated anomalies and chromosomal defects in CL, CP and CLP [Maarse et al., 2012]. Although several candidate genes and molecular pathways have been strongly implicated, we still do not have definitive causal mutations to explain the majority of cases. It now seems highly likely that NSCL/P aetiology may involve many more genes than previously predicted, making their study more difficult [Farrall and Holder, 1992; FitzPatrick and Farrall, 1993; Schliekelman and Slatkin, 2002; Christensen and Mitchell, 1996; Mitchell and Christensen, 1996] as well as confounding large scale genome-wide association studies (GWAS). Another possibility is that the mutations are mostly private, so are not detectable by GWAS methodologies. Furthermore, they most likely involve multiple gene interactions such that a defect results only when inherited on a permissive genetic background. Recent evidence is also pointing to another possibility, that mutations or cytogenetic disruption affecting specific cis-acting regulatory regions, often some considerable distance from the gene, may play a decisive role. In this model, loss-of-function coding mutations lead to a syndrome, usually involving a cleft, while down regulation of expression via a tissue-specific regulator, may result only in an isolated cleft.

Our understanding of the genetic basis underlying orofacial clefts is heavily biased in favour of our knowledge of the syndromic forms [Stanier and Moore, 2004]. A quick search of OMIM with the terms cleft lip or cleft palate returned more than 350 and 650 entries respectively, representing nearly 300 syndromes, an increasingly large proportion of which (~75%) now have an established genetic cause. Many of the more common syndromes and their causal genes were presented within a recent review [Leslie and Marazita, 2013]. Nevertheless, study of NSCL/P has proven to be much more refractory to the discovery of causal mutations. Although it makes sense that syndromic cases can be more easily collated into homogeneous study cohorts and it is clear that NSCL/P is therefore more heterogeneous, the lack of success has still been something of a surprise on a number of levels.

First, NSCL/P cases are more common and much effort has gone into the study of large cohorts of these patients including GWAS [Beaty et al., 2010; Ludwig et al., 2012; Böhmer et al., 2013; Ludwig et al., 2014]. Secondly, there is no shortage of families with a history of clefts, including many multiplex, multi-generation families (showing clear inheritance, albeit often without full penetrance), which have been subject to linkage techniques and recently whole exome sequencing strategies [Dixon et al., 2011; Ng et al., 2010a, 2010b; Mitchell et al., 2012]. Thirdly, various well-delineated syndromic index cases are reported to have close relatives carrying the same mutation but who only suffer from the cleft and without the family history would have otherwise been designated as non-syndromic [Vieira et al., 2005]. Where are these individuals when large-scale NSCL/P genetics projects are being conducted? On closer study, it now appears increasingly that NSCL/P cases may also present with and/or have relatives who carry a subclinical phenotype [Vieira et al., 2008c; Neiswanger et al., 2007; Suzuki et al., 2009; Weinberg et al., 2009; Schmidt et al., 2013].

The aim of this review is therefore to highlight some of the common abnormalities presenting with syndromic CL/P and the genes involved in those cases. This may provide information with which to better interrogate GWAS studies, whole genome sequencing strategies or cytogenetic analysis for loci external to coding regions that could be connected to NSCL/P.