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Chromosome 22q11.2 deletion may contain a locus for recessive early-onset Parkinson's disease

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Abstract

Recently, it has been reported that carriers of a hemizygous chromosome 22q11.2 deletion may be at increased risk of early-onset Parkinson's disease. Herein, we propose a hypothesis that it is not the microdeletion per se that is responsible for the phenotype but rather a complete loss of function of a gene within the region due to the combination of the deletion and another mutation on the alternate allele. Thus we propose the deletion may be highlighting a novel locus for a recessive form of early-onset Parkinson's disease

Keywords

early-onset; Parkinson's disease; PD; recessive; 22q11.2 deletion; genetic

Point of view

The chromosome 22q11.2 deletion syndrome (22q11.2DS), known as DiGeorge syndrome or velocardiofacial syndrome (OMIM#188400, #192430), causes variable phenotypic signs such as learning difficulties, congenital heart diseases, palatal abnormalities, laryngotracheoesophageal anomalies, characteristic facial features, immune deficiency, hypocalcemia and seizures. It is the most common human microdeletion syndrome and occurs in >1 in 4000 live births [1]. The vast majority of 22q11.2DS (approximately 90%) events occur *de novo*, however approximately 10% of this syndrome is inherited from a parent. The majority of the patients (approximately 85%) with the deletion share a common large 3 Mb hemizygous deletion including approximately 30–40 functional genes [1, 2]. Most affected children survive to adulthood and the diagnosis may be missed due to the significant variability of the phenotype, particularly due to the lack of typical findings [1].

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Recently, Butcher and colleagues reported four patients with early-onset Parkinson's disease (EOPD; mean age at onset 43.8±3.8, range 39–48) from a cohort of 159 adults with the chromosome 22q11.2 deletion [2]. Moreover two out of the three had displayed typical neuropathological features of Parkinson's disease (PD) with prominent Lewy bodies on autopsy examination [2]. The authors concluded chromosome 22q11.2 deletions may be a new genetic risk factor for EOPD, although the underlying pathogenic mechanism remains unclear. A further screening of 225 EOPD patients (age at onset ≤ 50 years) identified one additional carrier [2], thus Butcher and colleagues stressed the necessity of screening for chromosome 22q11.2 deletions in patients with EOPD to validate their findings. Interestingly, over the last 15 years three patients with the chromosome 22q11.2 deletion have been independently identified who also present with early-onset parkinsonism (ages at onset were <27, 42 and <42 years respectively). [3–5].

Given these findings further screening of EOPD patients is suggested for the chromosome 22q11.2 deletion, under the assumption it increases disease risk in the hemizygous state. However, EOPD is a relatively rare disorder and the majority of chromosome 22q11.2 deletion carriers do not present with signs of parkinsonism; therefore there may be more to the association than first appears. We propose it is not the microdeletion per se that is responsible for the phenotype, but rather the complete loss of function of a gene at the locus due to the combination of the deletion and a mutation on the other allele. To validate this hypothesis should be relatively straightforward, with the sequencing of genes located within the region in chromosome 22q11.2 deletion carriers with EOPD. This approach may help resolve the question of whether the deletion itself is increasing the risk or a specific gene located within this region is responsible. If a complete loss-of-function can be verified for a specific gene, that would then open the door for screening EOPD patients (without the chromosome 22q11.2 deletion) for other types of recessive mutations, which may be more frequent. Interestingly, the clinical phenotype, including the age at onset, parkinsonism and incontinence, looks relatively homogeneous in most of the six patients described suggesting a single genetic cause may exist[2–5].

It is clear that copy number variants play an important role in EOPD given previous findings with *PRKN*, *PINK1*, *DJ-1* and *SNCA* [6, 7]. The chromosome 22q11.2 deletion region contains some excellent candidate genes; *COMT*, encoding Catechol-O-Methyltransferase is involved in catecholamine catabolism including dopamine and thus plays a role in regulating dopamine levels; COMT-inhibitor has been used as a treatment for PD [8]. The deletion region also contains *SEPT5*, encoding SEPTIN5 which functionally interacts with PARKIN (encoded by *PRKN*) and *DGCR8* which encodes a subunit of a complex which mediates the biogenesis of microRNAs, including miR-185 (also encoded within the chromosome 22q11.2 deletion) which is predicted to target *LRRK2* [2].

Reduced penetrance is a common feature of neurodegenerative disease and this has been demonstrated for a number of dominant loci in PD, including *LRRK2*, *SNCA* and *VPS35* [9]. In addition, heterozygous *GBA* mutations are a well-established risk factor for Lewy body disease [10]. These findings highlight the complexity within phenotypic presentation of PD and suggest that it is likely that both genetic loci and environmental modifiers exist that could account for an age-related reduction in penetrance of specific disease-related

variation. Therefore the original hypothesis that the microdeletion itself causes haploinsufficiency of a gene that increases the risk of EOPD remains as valid.

The approach of examining patients with a defined genetic syndrome who present with the co-occurrence of parkinsonism is reminiscent of the Gaucher's disease and *GBA* mutation story in Lewy body disease [10]. One of the great benefits to this approach is that large EOPD pedigrees are not required and prioritized candidate patients to screen are already available. There is still a large majority of EOPD patients without a genetic cause and it has become more difficult to find large multigenerational EOPD families with either a recessive or dominant mode of inheritance. The hope is that novel sequencing technologies and approaches will advance our ability to find new genetic determinants of PD [9]. Unearthing these genes will be critical to our understanding of the disease mechanisms and drive subsequent therapeutic intervention strategies.

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- Chromosome 22q11.2 deletion
- Novel locus
- Recessive early-onset Parkinson’s disease
- Complete loss of function