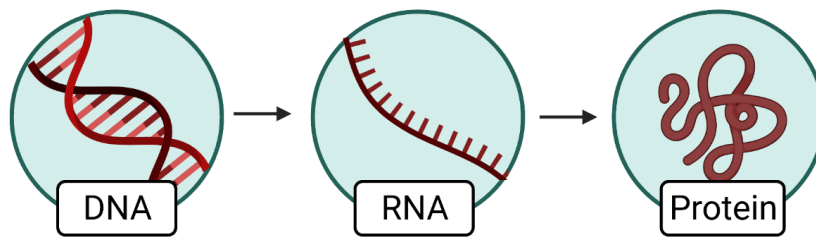


Understanding Your Genetic Report

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Basic Genetics of NR2F1:

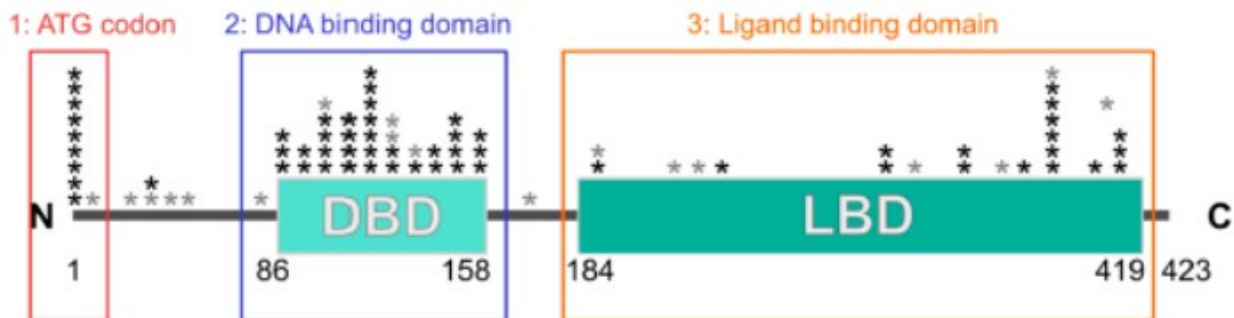
- *NR2F1* is a gene located on chromosome 5.
- The DNA in chromosomes provide instructions for making RNA for each gene.
- RNA of a gene provides instructions to make a specific protein.



- Proteins are long chains made up of a variety of different molecules called *amino acids*.
- Every protein made in cells has a different function to perform in cells.
- The *NR2F1* gene makes *NR2F1* RNA, which makes NR2F1 proteins.
- The NR2F1 gene in the DNA ultimately describes the NR2F1 protein that will be made.

There are Two Main Types of Genetic Mutations (aka variants):

1. Simple point mutations (aka missense mutations): This is a mutation causing a change of just one letter in the DNA. In Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS), these mutations occur most often in the:
 - DNA Binding Domain (DBD)
 - OR
 - Ligand Binding Domain (LBD)



2. Truncations: These are deletions in the DNA, or a specific type of point mutation in the DNA which prevent the full NR2F1 protein from being made. The different types are:
 - Mutations at the beginning of the gene (Start Codon).
 - “Nonsense” mutations

- “Frameshift” mutations

Translating Your Genetic Report:

1. Find in the report where the variant (aka mutation) in the *NR2F1* gene is reported.
 - ★ Usually, a small table identifying “Pathogenic Variants” is included on the first page of the report. The table might have categories like “Gene”, “Coding Sequence”, and “Amino Acid/ Protein Change”, among others.
 - ★ (The specific location of this information on the actual report will vary depending on the organization which performed the genetic testing.)
2. In this table, under the *NR2F1* gene, find the series of numbers and letters starting with “c.” and/or “p.”.
Notation using “c.” refers to the DNA. Notation using “p.” is referring to the protein.

Example:

c.123 T>C This describes a Point Mutation.

- In this example, this means that at position **123** in the coding (c.) DNA, the nucleotide (letter) in their DNA should be a **T** but has changed to a **C**.

p.F41S This is the same point mutation as above, just described in a different way.

- This describes the type of *amino acid* in the NR2F1 protein (p.). Here, the *amino acid* at position **41** of the NR2F1 protein changes from **F** to **S**.
- You don’t need to worry about the different amino acid letters or what they each stand for!

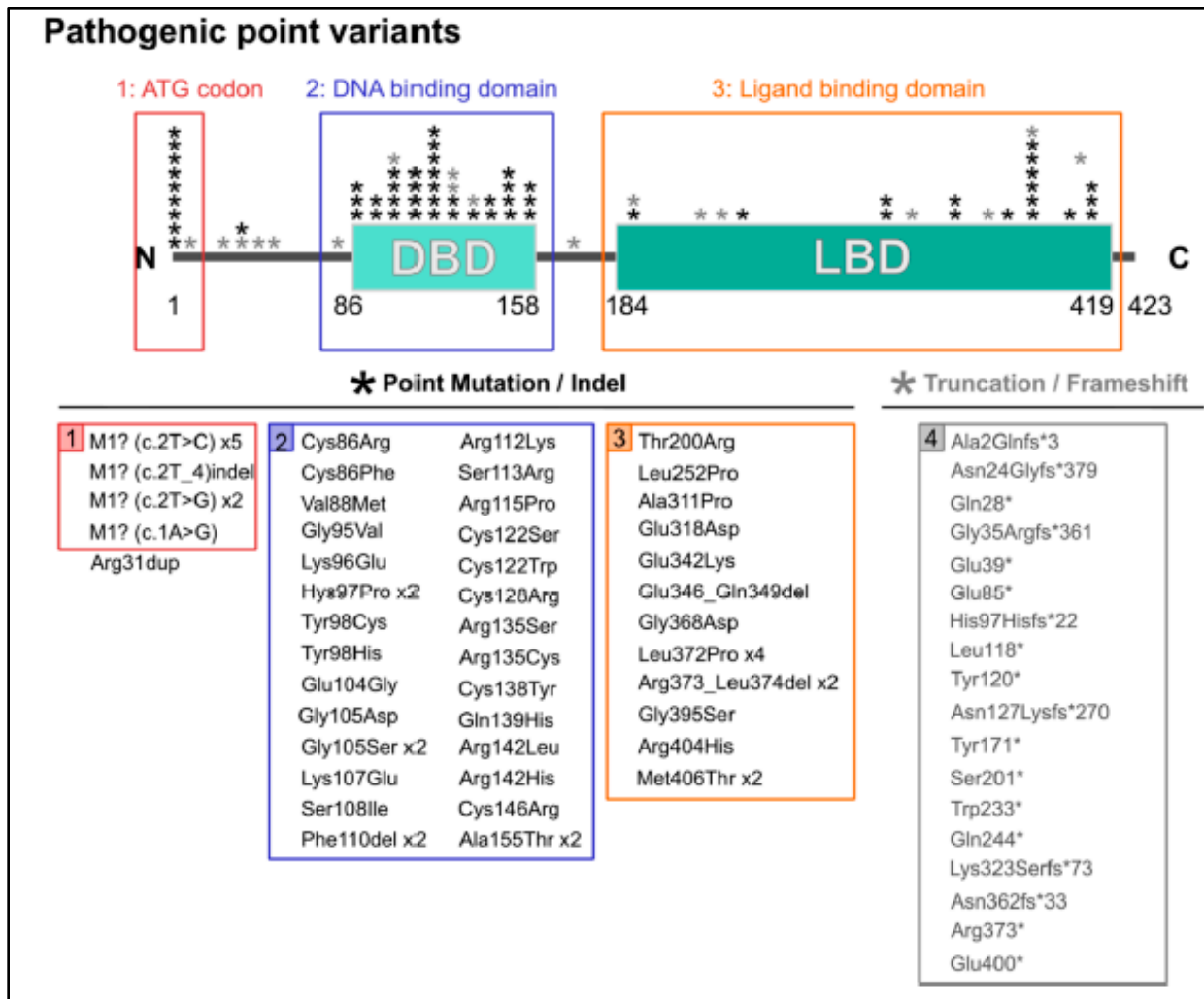
*** Beware that “c.” positions are not the same as the “p.” positions***

Other Examples:

- **M1?** c.2T>C, or anything similar using “**M1?**”, denotes a mutation in the Start Codon (aka ATG Codon).
- p.R**373**_L**374** **del** denotes a Deletion from position **373** to **374**.
- p.L**118*** or p.L**118****X** denotes a Nonsense Mutation at position **118**.
- p.A**2**Q **fs** denotes a Frameshift Mutation at position **2**.

3. Identify which example is closest to you and/or your child's. See Figure 1

Figure 1. Map of Known Mutations in the NR2F1 Protein:



(Figure taken from Bertacchi et al 2022)

Your and/or Your Child's Mutation to Other Patients:

Using the c. and p. information in your genetic report, along with the ranges below, you can classify almost every BBSOAS individual into one of six different groups:

1. Point Mutations in the DBD (p. 86 to 158)
2. Point Mutations in the LBD (p. 184 to 419)
3. Point Mutations in the Start Codon ("M1?")
4. Deletions ("del")
5. Frameshift mutations ("fs")
6. Truncations (* or X)

*** Note that “p.” locations are not the same as the “c.” locations!

Table 1. Outcomes of Patients with Similar Mutations:

	<i>All variants</i>	<i>Variants in the DBD</i>	<i>Variants in the LBD</i>	<i>Deletions</i>	<i>Variants in the Start Codon</i>	<i>Truncations</i>	<i>Frameshift</i>
	<i>(N = 92)</i>	<i>(N = 32)</i>	<i>(N = 17)</i>	<i>(N = 15)</i>	<i>(N = 9)</i>	<i>(N = 11)</i>	<i>(N = 7)</i>
Morphology							
<i>Myelin defects</i>	14.13%	25%	11.76%	6.67%	0%	18.18%	0%
	13/92	8/32	2/17	1/15	0/9	2/11	0/7
<i>Corpus callosum malformations</i>	32.61%	46.88%	0%	13.33%	33.33%	63.64%	42.86%
	30/92	15/32	0/17	2/15	3/9	7/11	3/7

	<i>All variants</i>	<i>Variants in the DBD</i>	<i>Variants in the LBD</i>	<i>Deletions</i>	<i>Variants in the Start Codon</i>	<i>Truncations</i>	<i>Frameshift</i>
	<i>(N = 92)</i>	<i>(N = 32)</i>	<i>(N = 17)</i>	<i>(N = 15)</i>	<i>(N = 9)</i>	<i>(N = 11)</i>	<i>(N = 7)</i>
Development & behavior							
<i>Developmental delay</i>	88.04%	90.62%	70.59%	93.33%	88.89%	90.91%	100%
	81/92	29/32	12/17	14/15	8/9	10/11	7/7
<i>Delayed motor development</i>	30.43%	40.63%	11.67%	20.00%	66.67%	9.09%	42.86%
	28/92	13/32	2/17	3/15	6/9	1/11	3/7
<i>Intellectual disability/ speech delay</i>	86.95%	93.75%	70.59%	86.67%	88.89%	90.91%	85.71%
	80/92	30/32	12/17	13/15	8/9	10/11	6/7
<i>Autism spectrum disorder (ASD)</i>	38.04%	40.63%	29.41%	26.67%	33.33%	45.45%	71.43%
	32/92	13/32	5/17	4/15	3/9	5/11	5/7
<i>ASD-like traits</i>	14.13%	28.13%	0.00%	6.67%	22.22%	0.00%	14.29%
	13/92	9/32	0/17	1/15	2/9	0/11	1/7
<i>ADHD (Attention deficit hyperactivity disorder)</i>	18.48%	9.38%	5.88%	26.67%	22.22%	36.36%	42.86%
	17/92	3/32	1/17	4/15	2/9	4/11	3/7

	<i>All variants</i>	<i>Variants in the DBD</i>	<i>Variants in the LBD</i>	<i>Deletions</i>	<i>Variants in the Start Codon</i>	<i>Truncations</i>	<i>Frameshift</i>
Visual System	(N = 92)	(N = 32)	(N = 17)	(N = 15)	(N = 9)	(N = 11)	(N = 7)
CVI (Cerebral visual impairment)	42.39%	53.13%	47.06%	26.67%	33.33%	27.27%	42.86%
	39/92	17/32	8/17	4/15	3/9	3/11	3/7
Optic atrophy	67.39%	78.13%	47.06%	53.33%	77.78%	72.73%	71.43%
	62/92	25/32	8/17	8/15	7/15	8/11	5/7
Optic nerve hypoplasia	21.74%	12.50%	29.41%	0.00%	44.44%	27.27%	57.14%
	20/92	4/32	5/17	0/15	4/9	3/11	4/7
Pallid or small optic disk (P/SOD)	19.56%	18.75%	11.76%	33.33%	22.22%	18.18%	14.29%
	18/92	6/32	2/17	5/15	2/9	2/11	1/7

	<i>All variants</i>	<i>Variants in the DBD</i>	<i>Variants in the LBD</i>	<i>Deletions</i>	<i>Variants in the Start Codon</i>	<i>Truncations</i>	<i>Frameshift</i>
Others	(N = 92)	(N = 32)	(N = 17)	(N = 15)	(N = 9)	(N = 11)	(N = 7)
Epilepsy	45.65%	62.50%	29.41%	26.67%	55.56%	45.45%	42.86%
	42/96	20/32	5/17	4/15	5/9	5/11	3/7
Hypotonia	61.96%	75.00%	35.29%	60.00%	88.89%	54.55%	57.14%
	57/92	24/32	6/17	9/15	8/9	6/11	4/7

(Tables adapted from Bertacchi et al 2022)

References:

1. Bertacchi, M.; Tocco, C.; Schaaf, C.P.; Studer, M. Pathophysiological Heterogeneity of the BBSOA Neurodevelopmental Syndrome. *Cells* 2022, 11, 1260. <https://doi.org/10.3390/cells11081260>